Risk of Perinatal Infection in Women with and without Systemic Lupus Erythematosus (SLE) and their Infants

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Abstract

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Introduction: Increased risk of adverse birth outcomes including preterm delivery is well described in women with systemic lupus erythematosus (SLE), but risk of infection in either mother or infant during the peripartum period is not well described. We conducted a population-based study to compare infection risk in women with and without SLE and their infants.

Methods: Linked birth-hospital discharge data identified all 1,396 deliveries to women with an ICD9 code indicating SLE in Washington State during 1987-2013. 5,584 women without SLE were identified for comparison, frequency-matched on delivery year. Maternal and infant infection during the birth hospitalization, and for infants, infection-related re-hospitalization in the first 30 days of life, were identified using birth and hospital discharge records. Relative risks (RR) and 95% confidence intervals (CI) for infection outcomes were estimated using Mantel-Haenszel stratified analysis, with adjustment for relevant covariates. The effects of gestational age in the relationships of maternal SLE to infant outcomes were assessed to better understand other mechanisms for infection aside from prematurity.

Results: Women with SLE were 1.51 times more likely (95% CI 1.29-1.77) to have an infection during the birth hospitalization and 1.23 times more likely (95% CI 1.09-1.40) to receive antibiotics during labor, although no increased risk was observed for chorioamnionitis specifically (RR 0.79, 95% CI 0.44-1.40). Infants of women with SLE had a RR for any infection during the birth hospitalization of 2.59 (95% CI 1.77-3.80) which was attenuated after adjustment for gestational age (RR 1.44, 95% CI 0.96-2.15). In general, RRs for neonatal infection, sepsis, and receipt of antibiotics were increased for infants of women

with SLE, but these RRs were markedly attenuated after adjustment for gestational age. No increased risk of infection-related infant re-admission within 30 days was observed.

Discussion: Women with SLE have increased risk of peripartum infections and antibiotic exposure. Their infants have a greater likelihood of infection during the neonatal period, although much of this association may be ascribed to increased risk of prematurity. Providers caring for pregnant women with SLE should be aware of the probable excess risk of infection in this maternal and neonatal population.

Introduction

Neonatal infections have potentially serious and long-term sequelae, including permanent neurosensory loss, developmental delay, and infant death.[1,2] Newborns are particularly vulnerable to infection due to the immaturity of their immune systems[2] and reliance on borrowed immunity from their mother in the form of circulating antibodies in the first few months of life. Women with systemic lupus erythematosus (SLE), a systemic autoimmune disease, frequently have compromised immunity, as a result of both the disease process itself as well as the immunosuppressive medications often prescribed for its management.[3] Persons with SLE are known to have a greater risk of infection, which may cause up to 25% of all deaths in this population.[4,5] The increased risk of infection in women with SLE is a potentially important consideration for neonatal health, as the baby is susceptible to "vertical" transmission of infection (transmission *in utero* or at the time of delivery) from the mother. Furthermore, it is biologically plausible that an immunocompromised state in the mother may lead to decreased placental transmission of protective immunoglobulin G (IgG) antibodies to the fetus[6], putting the neonate at additional risk for infection from external sources in the neonatal period. Although there is extensive literature characterizing poor pregnancy outcomes in women with SLE and their infants, few studies have addressed the risk of infection in the mother during the antenatal or postnatal periods[7,8], and to our knowledge, no studies have addressed infection risk in the infant during the neonatal period. Such studies could provide important information to healthcare providers of women with SLE for the purpose of both counseling and monitoring around the time of pregnancy. Our study was designed to evaluate the risk of perinatal infection and receipt of antibiotics in women with SLE compared to women without SLE, and to evaluate the risk of neonatal infection and exposure to antibiotics in their offspring.

Methods:

This is a population-based cohort study using linked birth certificate and hospital discharge data from Washington State from 1987-2013. Birth certificate data was linked to hospital discharge data from the Comprehensive Hospital Abstract Reporting System (CHARS), the state-wide hospital discharge database that includes all hospitalizations at non-government facilities in Washington State. As only de-

identified data were accessed, this study was determined to be exempt from Human Subjects Protection Committee review by the Washington State Institutional Review Board.

Women with Systemic Lupus Erythematosus (SLE) included those with either of two ICD-9 codes (695.4 “Lupus Erythematosus” or 710.0 “Systemic Lupus Erythematosus”) present in the hospital discharge record for the delivery hospitalization. All 1,396 women identified with SLE who had singleton deliveries during the study years were identified. For comparison, 5,584 women without SLE were selected randomly from the remaining singleton deliveries in the database, frequency-matched on year of delivery to women with SLE. In our initial evaluation of maternal characteristics and outcomes, we included all data pertaining to the delivery hospitalization, which included pregnancies that resulted in fetal deaths (23 women with SLE; 31 comparison women). To examine neonatal outcomes, only live births were included.

We evaluated the following maternal infection outcomes: chorioamnionitis, receipt of antibiotics during the labor, or a diagnosis of any infection coded for the maternal birth hospitalization. Chorioamnionitis was defined if either ICD9 code (762.7 or 658.4) was indicated in the hospital discharge record, or if the check box on the birth certificate indicated “Clinical chorioamnionitis or maternal temperature >38.0 during labor.” Maternal receipt of antibiotics was also ascertained by birth certificate checkbox for deliveries 2003 or later. The maternal infection outcome included all relevant ICD9 codes for infection (Appendix A) with the exception of dermatophytoses and HPV, which were not included due to being non-invasive infections, and asymptomatic bacteruria and Group B Strep colonization, which are infection risk factors rather than indicators of the presence of infection; all other possible infections including bacterial, viral, parasitic, and fungal infections were included.

Offspring outcomes were restricted to the neonatal period, defined as the first 30 days of life, for several reasons. We were interested in whether compromised immunity in the mother may lead to increased infection risk in the baby, and such a risk would be greatest in the neonatal period when the baby is most reliant on the mother’s transplacentally-derived immunoglobulins for protective immunity. Additionally, because infections following the birth hospitalization were ascertained only in hospitalized babies, the ascertainment of these in our study would be nearly complete only during the neonatal period. We evaluated the following outcomes in neonates: infection during the birth hospitalization, receipt of anti-

sepsis antibiotics during the birth hospitalization as indicated by birth certificate checkbox, infection indicated in any subsequent hospitalization within the neonatal period, any infection within 30 days of life ("neonatal infection"), and neonatal sepsis. Neonatal infection was a composite outcome of infection during the birth hospitalization and infection associated- subsequent readmissions within 30 days of birth. Neonatal sepsis included a subset of the neonatal infection outcome, but was limited to ICD9 codes that included the terms "sepsis," "septecemia," or "bacteremia." Admission to the Neonatal Intensive Care Unit (NICU) was also evaluated. Infections during the birth hospitalization and during rehospitalization were determined through an exhaustive list of hospital discharge ICD9 codes (the same ICD9 criteria used to determine maternal infection; see Appendix A). Receipt of antibiotics and admission to the NICU were identified from birth certificate check boxes for deliveries 2003 or later.

A stratified analysis for the risk of these infection-related outcomes was performed to compare the experiences of women with and without SLE using Mantel-Haentzel relative-risk (RR) estimates and their 95% confidence intervals (CI). Variables considered for their potential effects on such relationships included delivery year, maternal age (<20, 20-34, 35+ years), prenatal smoking (yes/no), maternal education (less than high school, high school, college, or graduate education), gestational age at delivery (<37 weeks, 37 to <42, >=42 weeks), number of prior deliveries (0, 1, 2+), number of prior pregnancies (0,1,2+), race/ethnicity (white, black, Asian/Pacific Islander, Hispanic and other), cesarean-section delivery (yes/no), diabetes (yes, including prevalent and gestational/no), and whether or not the infant was being breastfed at discharge from the birth hospitalization (yes/no). Subsequently, term and post-term births were combined into a single category, as the study contained only 5 post-term deliveries in the SLE group. Prevalent and gestational diabetes were combined, as the presence of hyperglycemia due to either entity plausibly poses a similar increased risk for infection, and when separated, the numbers were too small for adequate evaluation. Birth weight was evaluated as a potential effect modifier for infant outcomes, but it was not evaluated as a confounder due to the high degree of collinearity with gestational age (there was 87% agreement between birth weight category and gestational age in our cohort), which would complicate evaluation of both variables simultaneously. Confounding was considered to have occurred when > 10% change between crude and univariately adjusted RRs was found. Effect modification was evaluated by χ^2 tests of homogeneity and the presence of important differences in the

RRs between strata. For maternal outcomes, potential confounding or effect modification by diabetes and BMI was evaluated using subgroup analyses, as these data were only available after 2002. For the same reason, a subgroup analysis was performed for neonatal outcomes to evaluate for potential effect modification or confounding by maternal diabetes or breastfeeding.

Maternal or infant length of stay (LOS) during the delivery hospitalization was not included as a potential confounder or effect modifier because of its complicated relationship to infection; longer LOS may be in the causal pathway leading to nosocomial infections, but it also may be a consequence of infection. Therefore, we performed a separate analysis of the relationship between maternal SLE and LOS in both mothers and infants, stratified by reported presence or absence of infection during that hospitalization.

RESULTS:

Women with and without SLE were similar with respect to BMI, the presence of diabetes, Group B Strep culture positivity, and parity (Table 1). Women with SLE were older, had a greater number of prior pregnancies, were less likely to be white, unmarried, or to smoke, were more highly educated, had a greater likelihood of having a cesarean-section, and had a longer length of stay during the birth hospitalization. Infants of women with SLE were slightly less likely to have been breastfed prior to discharge and were more likely to be premature, low birth-weight, and have a longer birth hospitalization as compared to infants of women without SLE.

Following adjustment for maternal age and cesarean-section, the risk of infection during the delivery hospitalization was 1.51 times greater (95% CI=1.29-1.77) in women with SLE compared to women without SLE (Table 2). The adjusted risk of receiving antibiotics at delivery was 1.23 times greater (95% CI=1.09-1.40) in women with SLE compared to women without SLE. In subgroup analysis of observations between 2003 - 2013, among underweight and normal weight women, those with SLE were 1.44 times more likely to receive antibiotics during labor (95% CI=1.20-1.72) compared to women without SLE. Among overweight women, no increased risk for antibiotic use in women with SLE was observed (RR=1.09, 95% CI=0.89-1.34) (data not shown). No increased risk of chorioamnionitis during the birth hospitalization was observed for women with SLE (RR=0.79, 95% CI=0.44-1.40).

All infant outcomes were adjusted for maternal age. Among infants, the RR for any infection during the birth hospitalization was 2.59 (95% CI=1.77-3.80) in babies born to women with SLE (Table 3). After adjustment for gestational age, the RR was attenuated (RR=1.4, 95% CI=0.96-2.15). Similarly, in babies born to women with SLE, the RR for receiving anti-sepsis antibiotics during the birth hospitalization was 2.13 (95% CI 1.31-3.46), but after adjustment for gestational age the RR was 1.28 (95% CI=0.74-2.22). No increased risk of infection-related rehospitalization within 30 days was observed (RR=1.00, 95% CI=0.54-1.88; gestational age-adjusted RR=0.98, 95% CI =0.49-1.96). The risk of any infection within 30 days from birth (neonatal infection) was 1.81 times greater in babies born to of women with SLE (95% CI=1.30-2.51), but there was no evidence of excess risk after adjustment for gestational age (RR=1.18, 95% CI=0.83-1.70). Similarly, neonatal sepsis was more frequent in babies born to women with SLE (RR=2.33, 95% CI= 1.49-3.64), but this association decreased after adjustment for gestational age (adjusted RR=1.32, 95% CI=0.82-2.12).

Among infants of women who smoked during pregnancy, risk of NICU admission was 6.22 times greater (95% CI=3.40-11.39) in babies born to women with SLE compared to those born to women without SLE, and this association remained present to a considerable degree after adjustment for prematurity (RR 3.20, 95% CI=1.75-5.86). Among babies born to women who did not smoke during pregnancy, RR for NICU admission in infants of women with SLE was 2.47 (95% CI=1.92-3.17), and this RR decreased to 1.24 (95% CI=0.99-1.54) after adjustment for prematurity. In subgroup analysis of observations between 2003 – 2013, neither maternal diabetes status nor breastfeeding affected these associations (after evaluation for both potential confounding and effect modification).

Following adjustment for delivery by cesarean-section, women with SLE had greater risk of longer length of stay for the birth hospitalization, whether or not a diagnosis of infection was made (Table 4). Among infants without infection, those of women with SLE were more likely to have a longer length of stay. Among infants with a diagnosis of infection, having a longer length of stay did not depend upon whether the mother had SLE.

DISCUSSION

These results suggest that women with SLE have a greater infection risk in the perinatal period as compared to women without SLE. This finding is consistent with results of the few prior studies that have investigated this topic. Bauer et al[7] studied 4,158 women whose delivery hospitalization was affected by severe sepsis and found SLE to be an independent risk factor (adjusted OR 9.4, 95% CI 5.2-16.7), accounting for 1.4% of all cases of severe sepsis in that study. Similarly, Clowse et al[8] found that the incidence of sepsis during the delivery hospitalization was 0.5% in women with SLE vs. 0.1% in women without SLE (OR 3.5, 95% CI 2-6), and the incidence of pneumonia was 1.7% in women with SLE vs. 0.2% in those without SLE (OR 4.3, 95% CI 3.1-5.9). Plausible mechanisms for increased infection risk in women with SLE include treatment with immunosuppressive therapies as well as immune dysregulation from the disease process itself[3].

Although prematurity is both a known risk factor for neonatal infection[9] and a known complication of SLE in pregnancy[10-13], to date the risk of infection in infants born to women with SLE has not been elucidated. In the present study, infants of affected mothers had a greater risk of infection and of admission to the NICU during the birth hospitalization, as well as a greater risk of sepsis or any infection in the neonatal period. Notably, much of this excess risk appeared to be due to prematurity. In a systematic review and meta-analysis of pregnancy outcomes in women with SLE, the frequency of premature birth in women with SLE was 39.4%.[14] The infant's immune system is deficient early in life due to several mechanisms, including a decreased ability to produce inflammatory cytokines such as TNF-α and IL6, reduced neutrophil and dendritic cell function, decreased activation of natural killer cells, and minimal production of circulating immunoglobulins.[3] Thus, protective immunity for the infant is dependent upon placental transfer of the mother's circulating IgG. Passage of IgG from the mother to the baby increases dramatically with advancing gestational age[2], which partly explains why pre-term infants have greater infection risk. In our study, prematurity was likely a major mechanism leading to infection in neonates of women with SLE. After adjusting for gestational age to assess mechanisms other than prematurity, risk estimates for infection during the birth hospitalization, infection or sepsis in the neonatal period, and receipt of anti-sepsis antibiotics remained increased, but were considerably attenuated. Due to the broad indications for NICU admission, NICU admission is not a perfect surrogate for infection risk.

However, understanding the risk of NICU admission may be helpful for counseling women with SLE in the perinatal period.

This study had several limitations. The reliance on ICD 9 codes to identify SLE likely led to misclassification; the use of ICD9 codes to identify persons with SLE has been shown previously to have a positive predictive value of 70-90%[15]. We were also unable to assess any disease characteristics of women with SLE such as severity, presence of organ involvement, or treatment regimen, thus precluding the possibility of identifying clinical features that might correlate most strongly with risk of infection. Reliance on both ICD9 codes and birth certificate data for assessment of our outcomes could also have led to misclassification, and we were unable to adjudicate discrepancies between birth certificate and hospital discharge data due to the nature of these databases. Additionally, the possibility of residual confounding remains, even after consideration of and adjustment for the many factors considered here. Furthermore, due to small numbers in some analyses, our ability to identify associations of small to moderate size was limited. Lastly, due to the rarity of these infection-related outcomes, it is possible that this study was underpowered to detect increased risk caused by mechanisms other than prematurity.

In conclusion, women with SLE have an increased risk of peripartum infections and antibiotic exposure compared to women without SLE. Also, their infants have a greater risk of infection during the neonatal period and a higher likelihood of admission to the NICU, in large part due to an increased risk of prematurity. Providers caring for women with SLE should be aware of these risks as they monitor patients during pregnancy and care for their infants. Future studies utilizing larger cohorts with detailed information about infection-related outcomes would be useful in order to further characterize these risks. Ideally, such studies would be adequately powered to allow for analysis of risk related to specific SLE disease characteristics or treatment regimens.

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Table 1. Characteristics of women with and without systemic lupus erythematosus (SLE) with deliveries in Washington state, 1987 – 2013, and their singleton infants.

	Women with SLE (N=1,396)		Women without SLE (N=5,584)	
Maternal Characteristic at delivery	N	%	N	%
Age (years)				
<20	39	2.79	503	9.01
20-29	627	44.91	2,894	51.83
30-34	457	32.74	1,389	24.87
35-39	222	15.90	651	11.66
40+	51	3.65	147	2.63
Unknown	*0*		*0*	
Race				
White	958	70.18	4,009	73.52
Black	87	6.37	221	4.05
Asian/Pacific Islander	165	12.09	482	8.84
Hispanic	97	7.11	606	11.11
Native American	58	4.25	135	2.48
Other Non-White	0	0	0	0
Unknown / refused to answer	*31*		*131*	
Body Mass Index*				
<18.5	27	3.91	98	3.53
18.5-24.9	327	47.39	1,284	46.19
25-29.9	160	23.19	741	26.65
>=30	176	25.51	657	23.63
Unknown	*75*		*280*	
Diabetes**				
No	700	93.33	2,809	93.54
Yes	50	6.67	194	6.46
Unknown	*15*		*57*	
Education Level				
Less Than High School	107	8.73	901	18.45
Graduated High School	281	22.94	1,316	26.95
College	678	55.35	2,197	44.98
Graduate School	159	12.98	470	9.62
Unknown	*171*		*700*	
Marital Status				
Unmarried	361	25.90	1,705	30.60
Married	1,033	74.10	3,866	69.40
Unknown	*2*		*13*	
Smoking During Pregnancy				
No	1,205	89.19	4,760	87.26
Yes	146	10.86	695	12.74
Unknown	*45*		*129*	

Group B Strep culture positive*				
No	614	81.87	2,453	81.68
Yes	136	18.13	550	18.32
Unknown	*15*		*57*	
C-Section				
No	890	63.75	4,263	76.37
Yes	506	36.25	1,319	23.63
Unknown	*0*		*2*	
Number of prior births				
0	574	41.90	2,278	41.51
1	437	31.90	1,763	32.12
2+	359	26.20	1,447	26.37
Unknown	*26*		*96*	
Number of prior pregnancies				
0	387	28.31	1,761	32.18
1	337	24.65	1,537	28.08
2+	643	47.04	2,175	39.74
Unknown	*29*		*111*	
Length of Stay at Birth Hospitalization				
<3 days	728	52.15	4,137	74.09
3-4 days	447	32.02	1,265	22.65
5-7 days	115	8.24	139	2.49
>=8 days	106	7.59	43	0.77
Unknown	*0*		*0*	

Infant characteristic, singleton live births only	Infants Born to Women with SLE N= 1,373		Infants Born to Women without SLE N= 5,553	
	N	%	N	%
Infant Breastfed during Birth Hospitalization***				
No	93	13.10	228	7.85
Yes	617	86.90	2,676	92.15
Unknown	*44*		*134*	
Birthweight (grams)				
<1500	60	4.39	44	0.79
1500-2499	227	16.62	194	3.50
2500-3999	1,015	74.30	4,625	83.54
≥4000	64	4.69	673	12.16
Unknown	*7*		*17*	
Gestational Age at Birth (weeks)				
<37	303	22.97	341	6.41
37- <42	1,011	76.65	4,884	91.86
>= 42	5	0.38	92	1.73

Unknown	*54*		*236*	
Length of Stay at Birth Hospitalization				
<3 days	822	62.46	4,297	80.71
3-4 days	267	20.29	797	14.97
5-7 days	66	5.02	96	1.80
>=8 days	161	12.23	134	2.52
Unknown	*57*		*229*	

*BMI and Group B Strep data available from 2003-2013 only; mothers with SLE: n= 765; mothers without SLE: n= 3,060

**Including gestational diabetes. Data available from 2003-2013 only; mothers with SLE: n= 765, mother's without SLE: n= 3,060

*** Infant breastfeeding data available from 2003-2013 only; infants of SLE mothers: n= 754, infants of mothers without SLE: n= 3,038

Table 2: Infection-related outcomes during the delivery hospitalization among women with and without systemic lupus erythematosus (SLE), Washington State, 1987-2013

	Women with SLE N=1,396		Women without SLE N=5,584			
Outcome	n/total	(%)	n/total	(%)	RR [a]	(95% CI)
Any infection	189/1396	(13.54)	470/5584	(8.42)	1.51[b]	(1.29-1.77)
Chorioamnionitis	14/1396	(1.00)	72/5584	(1.29)	0.79	(0.44-1.40)
Received antibiotics[c]	225/744	(30.24)	698/2989	(23.35)	1.23[b]	(1.09-1.40)

[a] All outcomes adjusted for age
[b] Adjusted also for c-section
[c] Data available for years 2003-2013 only

Table 3 : Infection-related outcomes in infants of women with and without systemic lupus erythematosus (SLE), Washington State, 1987-2013

	Women with SLE N= 1,319		Women without SLE N=5,317					
Outcome	n/total	%	n/total	%	RR[a]	(95% CI)	RR[a] adjusted also for gestational age	95% CI
Any infection during the birth hospitalization	43/1,319	3.26	69/5,317	1.30	2.59	(1.77-3.80)	1.44	(0.96-2.15)
Received sepsis antibiotics [b]	24/729	3.29	47/2,950	1.59	2.13	(1.31-3.46)	1.28	(0.74-2.22)
Infection-associated readmission within 30 days after birth.	12/1,319	0.91	53/5,317	1.00	1.00	(0.54-1.88)	0.98	(0.49-1.96)
Neonatal infection	51/1,319	3.87	120/5,317	2.26	1.81	(1.30-2.51)	1.18	(0.83-1.70)
Neonatal sepsis	30/1,319	2.27	58/5,317	1.09	2.33	(1.49-3.64)	1.32	(0.82-2.12)
NICU admission in infants of women who smoked[b]	25/66	37.88	18/274	6.57	6.22	(3.40-11.39)	3.20	(1.75-5.86)
NICU admission in infants of women who didn't smoke[b]	90/658	13.68	145/2,658	5.46	2.47	(1.92-3.17)	1.24	(0.99-1.54)

[a] All outcomes adjusted for maternal age
[b] Data available for years 2003-2013 only

Table 4: Risk of a prolonged length of stay (LOS)[a] during the delivery hospitalization in women with SLE vs. those without SLE, and their infants.		
	RR[b]	95% CI
Women		
All mothers	1.51	(1.42-1.60)
Without infection	1.51	(1.42-1.61)
With infection	1.35	(1.18-1.53)
Infants		
All infants	1.41	(1.29-1.53)
Without infection	1.43	(1.31-1.56)
With infection	0.97	(0.81-1.15)

[a] Relative risk of LOS >=3 days vs <=2

[b] Maternal LOS adjusted for delivery by cesarean section, and infant LOS adjusted for gestational age at birth.

Appendix A: ICD9 Codes for infection	
001-005, 032-041	Bacterial infections
006-007	Amebic, protozoal infections
008-009	Other enteric infections
010-018, 030-031	Tuberculosis and other mycobacteria
020-027	Zoonotic infections (mainly bacterial)
042+	HIV- excluded from IRB approval
080-088	Arthropod-borne diseases
090-099	Sexually transmitted infections
100-104	Spirochetal diseases
111-118	Fungal diseases
120-128	Nematode, trematode, cestode infections
130-134	Parasites, ectoparasites
136-139	Unclassified/other infections
320, 321.1-3, 321.8, 322.9, 323, 324	Meningitis/central nervous system infection
360.0, 372.0, 373.3-6, 376.0	Infections of the eye and orbit
382, 384.0-1, 386.35,460-465, 473	Ear, Nose, and throat infections
421, 422.92, 424.9	Cardiac infections
480-484, 486-488, 510	Pulmonary infections
567, 569, 573.1-2, 575.0-1	Gastrointestinal infections
590, 595.9, 599.0	Genitourinary infections
614, 616.0-1, 646.6, 647, 655, 658.4, 659.3, 670, 675, 760.2, 762.7	Infections of the reproductive tract and any “infection complicating pregnancy or delivery”
680, 682, 683, 684, 686.8, 686.9	Dermatologic infections
711.4-99, 730	Orthopedic infections
665.30, 771	“Damage to fetus from maternal infection.” Perinatal or congenital infections
790.7, 790.8	Bacteremia or viremia NOS
995.91, 995.92	Sepsis NOS, Septic shock
998.5, 999.3	Post-operative infection or infection complicating medical care