

Sepsis in Canadian children: a national analysis using administrative data

Graham C Thompson¹
Niranjan Kissoon²

¹Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada; ²British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada

Background: Severe infection resulting in sepsis is recognized as a leading cause of morbidity and mortality worldwide. The purpose of this study is to use longitudinal, population-based data to report national-level hospital metrics, providing a current assessment of the status of sepsis hospitalizations in Canadian children.

Methods: We performed an analysis of previously abstracted data from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). Children aged 0–17 years at the time of hospital admission were identified from a cohort of patients with sepsis or severe sepsis using the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-CA) and the Canadian Classification of Health Interventions (CCI). Descriptive population-based statistics are reported.

Results: Hospitalization data for 20,130 children admitted over 5 years were reviewed. The majority of children were young, with neonates (56.3%) and infants under 2 months (18.8%) representing the majority of cases. A decline in age-adjusted hospitalization rates was demonstrated in both overall and non-severe sepsis across the study period; however, no change was demonstrated for severe sepsis. While overall in-hospital crude mortality rates did not change significantly across the study period (range 5.1%–5.4%), a significant decrease was found in children aged 3–23 months and adolescents. Multi-organ failure was reported in more than one-quarter of children with severe sepsis. Odds of mortality increased significantly with number of organs failed.

Conclusion: Sepsis remains an important cause of morbidity and mortality in Canadian children, posing a significant burden on health care resources. Age continues to be associated with the incidence and severity of illness. Overall hospitalization rates have declined over time, as has mortality in severe sepsis. This report provides baseline metrics for future outcome-based research in Canada targeting prevention strategies and early diagnosis, as well as therapies preventing and managing organ failure.

Keywords: septic shock, child, hospitalization, mortality, epidemiology

Introduction

Severe infection resulting in sepsis is recognized as a leading cause of morbidity and mortality worldwide.^{1–3} The incidence of sepsis in developed nations has been increasing while overall mortality is decreasing, but still remains high.^{3,4} A recent population-based review of the status of sepsis hospitalization in the general population (all ages) across Canada determined a crude mortality rate of 30.5% in 2008–2009.⁵ Moreover, morbidity in survivors is often functionally devastating, and may include neurological impairment, chronic organ dysfunction, increased days admitted to hospital, and high

Correspondence: Graham C Thompson
Alberta Children's Hospital,
University of Calgary, 2888 Shaganappi
Trail NW, Calgary, T3B 6A8 AB, Canada
Tel +1 403 955 7295
Fax +1 403 955 7552
Email graham.thompson@albertahealthservices.ca

rates of mortality postdischarge.^{6–9} Emotional, social, and financial costs to individuals and health care systems are immense.^{10–12}

Recent administrative database analyses indicate that hospitalization rates for severe sepsis have significantly increased amongst adults in the US, while overall mortality rates have decreased.¹³ However, a dramatic difference in terms of incidence and mortality related to sepsis has been shown in the pediatric population when compared to adults. Previous studies from developed nations have shown a decrease in pediatric mortality related to sepsis to <10% in the early 2000s.³ Advancements in preventative care, including population-wide immunization practices and routine postnatal care guidelines, have likely made significant contributions to these noted improvements. Likewise, optimizing management in health care centers through liberal use of fluid resuscitation, early antibiotics, and intensive care management has improved patient outcomes.^{14–18}

Despite the successes of these primary care initiatives, children in developed and developing countries alike continue to suffer from the consequences of sepsis.⁷ As such, there has been renewed interest in resuscitation efforts and advanced management strategies in the care of the septic child. To optimize interventions and build capacity in any setting, an understanding of the current burden and disease trends is vital. However, robust information to guide Canadian pediatric initiatives is currently lacking.

The purpose of this study is to use longitudinal, population-based data in order to report national-level hospital metrics, providing a current assessment of the status of sepsis hospitalizations in Canadian children. This data is intended to represent the current burden of sepsis in children in Canada and will be used as baseline data to which future outcome-based improvement interventions can be compared.

Methods

We performed a pediatric-specific analysis of previously abstracted data⁵ from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). CIHI is a national administrative data repository. All data provided to CIHI by Canadian hospitals is done on a voluntary basis. Data from the province of Quebec is not included in this analysis due to differences in data collection format and processes.

Details of the initial data abstraction have been previously described by Husak et al.⁵ A description of the methods specific to this secondary analysis is given below.

Study setting

Geographically, Canada is the world's second largest country comprised of ten provinces and three territories. The estimated population in Canada (in millions) during the years 2004–2008 were 31.941, 32.245, 32.576, 32.927, and 33.318, respectively (<http://www5.statcan.gc.ca/cansim/>). Health care in Canada is publicly funded and governed nationally by the Canada Health Act, while services are provided under the jurisdiction of the provincial or territorial governments.

Study population

Children aged 0–17 years at the time of hospital admission were identified from a cohort of patients with sepsis or severe sepsis (see definitions below). The initial cohort was determined using the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-CA) and the Canadian Classification of Health Interventions (CCI) (Table S1). Children were classified into the following age groups based on age at time of hospital admission: neonates (newborns that had not been discharged from hospital), young infants (0–2 months), older infants (3–23 months), preschool (2–4 years), school-aged (5–12 years), and teen (13–17 years). Patients whose sex was not recorded as “male” or “female”, who were not admitted to acute care hospitals, or were not Canadian residents were excluded. Those with missing or invalid health card numbers, date of birth, and admission or discharge dates (required to construct episodes of care) were also excluded.

Time frame

Data were abstracted and grouped according to fiscal year, defined as April 1–March 31. Hospitalizations meeting the identified criteria of sepsis/severe sepsis with an admission date during fiscal years 2004/2005–2008/2009 were included.

Definitions

Sepsis, severe sepsis, and organ dysfunction definitions remained consistent with those used in the original database by Husak et al.⁵ Sepsis was defined using ICD-10-CA codes (Table S1). Severe sepsis was defined as sepsis with organ dysfunction in at least one of six systems, a definition typically used to define severe sepsis in administrative databases. Organ dysfunction was defined using ICD-10-CA codes and CCI codes (Table S2). The analysis was performed using one episode of care (defined as all contiguous inpatient acute care hospitalizations) as the base unit. Transfers from one center to another were accounted for by merging data; a transfer was assumed if admission to an acute care institution occurred on the same day or prior to discharge from the preceding acute

Table 1 Characteristics of pediatric patients hospitalized with sepsis in Canada between 2004 and 2009

	Sepsis – all comers			Severe sepsis n (% severe sepsis, % all sepsis by age)
	Male, n (%)	Female, n (%)	Total, n (%)	
Neonates	6,312 (55.7)	5,013 (44.3)	11,325 (56.3)	2,605 (58.7, 23.0)
0–2 months	2,193 (57.9)	1,594 (42.1)	3,787 (18.8)	648 (14.6, 17.1)
3–23 months	931 (54.3)	782 (45.7)	1,713 (8.5)	335 (7.6, 19.6)
2–4 years	537 (54.2)	453 (45.8)	990 (4.9)	202 (4.6, 20.4)
5–12 years	704 (54.8)	580 (45.2)	1,284 (6.4)	303 (6.8, 23.6)
13–17 years	536 (52.0)	495 (48.0)	1,031 (5.1)	347 (7.8, 33.7)
Total	11,213	8,917	20,130 (100)	4,440 (100, 22.1)

care institution. For episodes with transfers between facilities, transactions were linked regardless of the most responsible diagnosis following the index admission. Length of stay (LOS) was calculated for episodes of care (from the time of the first admission till the last discharge time).

Statistical analysis

Descriptive population-based statistics are reported including proportions, means, and medians as appropriate. Odds ratios with 95% confidence intervals are reported where applicable. Rates of hospitalization are reported per 100,000 children. Linear regression was used to examine trends across the study period.

Crude mortality rates are reported by severity of disease, as well as by age group.

Results

Hospitalization data for 20,130 children aged 0–17 years with any diagnosis of sepsis during the 5-year study period were available for review. The majority of children were young,

with neonates and infants under 2 months representing the majority of cases (56.3% and 18.8%, respectively). Males were more representative across all age groups. After the newborn period, severe sepsis demonstrated an increasing percentage of overall sepsis rates (Table 1 and Figure 1).

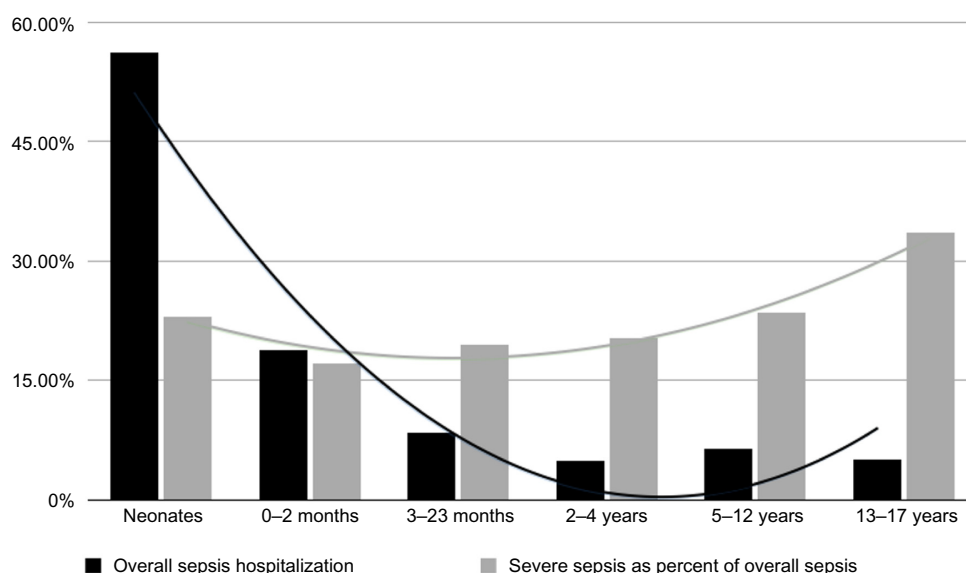
A decline in age-adjusted hospitalization rates was demonstrated in both overall and non-severe sepsis across the study period; however, no change was demonstrated for severe sepsis (Figure 2).

Organ failure

Table 2 reports the occurrence and mortality rates corresponding to the reported failure of individual organ systems. Multi-organ failure was reported in more than one-quarter of children with severe sepsis. Odds of mortality increased with number of organs failed (Table 3).

Mortality

While overall in-hospital crude mortality rates did not change significantly across the study period (range 5.1%–5.4%),

**Figure 1** Comparison of percent of sepsis hospitalizations by severity and age.

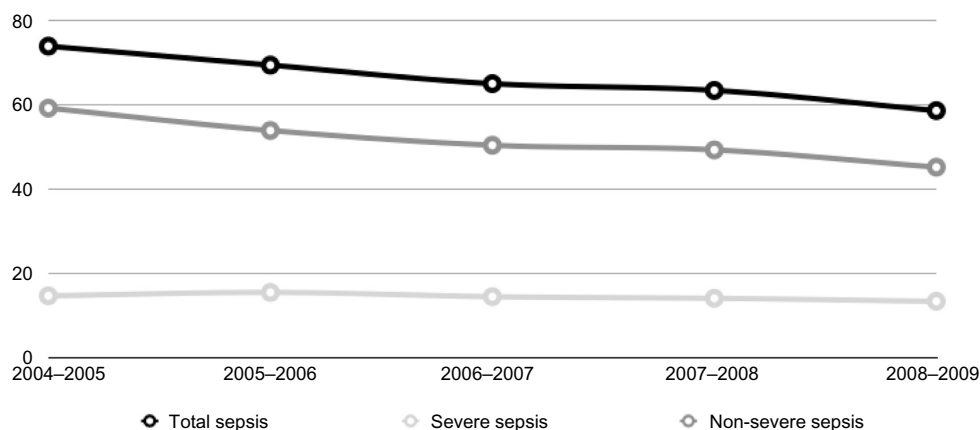


Figure 2 Age-adjusted hospitalization rates per 100,000 Canadian children.

a significant decrease in those with severe sepsis occurred (Figure 3). This reduction in mortality is attributed to declining mortality in two specific age groups; older infants (3–23 months) and adolescents (13–17 years; Figure 4).

Hospital length of stay

Data reporting hospital LOS were available only for the fiscal year 2008–2009. Overall LOS and intensive care unit (ICU) LOS are shown in Table 4, along with the proportion of children admitted to the ICU.

Discussion

To our knowledge, this is the first nation-wide epidemiologic report of sepsis amongst Canadian children. Our data shows that sepsis continues to be a significant health concern, with approximately 4,000 admissions and 200 deaths per year. We have demonstrated a significant decline in age-adjusted hospitalization rates for all children with diagnostic codes for sepsis, while crude mortality rates in this population remained constant over the 5-year reporting period. Conversely, the mortality rate for children diagnosed with severe sepsis declined despite constant age-adjusted hospitalization. This may be explained by increased awareness of sepsis, more aggressive early man-

agement, or improved access to intensive care facilities. Children with sepsis-related hospitalizations were found to have prolonged hospital LOS, and those with multiple organ failure were much more likely to die during their hospital stay.

As per similar studies of pediatric sepsis in developed countries,^{19–21} age plays a role in the epidemiology of disease; the neonatal population is significantly overrepresented. More than half of Canadian children diagnosed with sepsis are newborns, and 75% are <2 months of age. Similarly, 40% of children with severe sepsis were under 2 months. Interestingly, for those children in our cohort who were discharged from hospital after birth, severity of illness was associated with older age.

While Watson and Carcillo reported an increased incidence of severe sepsis in infant boys compared to girls,²² we found that the sex difference spanned all age groups. Ghuman et al have also reported sex-related differences in children with sepsis, demonstrating an increase in mortality and initial severity of disease, although differences were based on pubertal status.²³ To our knowledge, the exact mechanism of the sex differences is still to be determined, although a hormonal mechanism via androgen suppression has been postulated.²⁴

Table 2 Organ failure in Canadian children hospitalized with severe sepsis between 2004 and 2009

Organ system	n (%)	Mortality, %
Respiratory	691 (81.2)	17.5
Cardiovascular	202 (23.7)	21.3
Hematologic	103 (12.1)	26.2
Renal	96 (11.3)	25.0
Hepatic	25 (2.9)	56.0
Central nervous system	18 (2.1)	50.0

Table 3 Occurrence and mortality associated with organ dysfunction in Canadian children hospitalized for severe sepsis between 2004 and 2009

Number of organs failed	n (%)	Mortality, %	Odds ratio (95% CIs)
1 system	623 (73.2)	12.5	1.0
2 systems	188 (22.1)	27.1	7.2 (3.6–14.3)
3 systems	40 (4.7)	42.5	52.9 (29.3–95.4)

Note: 95% CIs: upper and lower limits on 95% CI.
Abbreviation: CI, confidence interval.

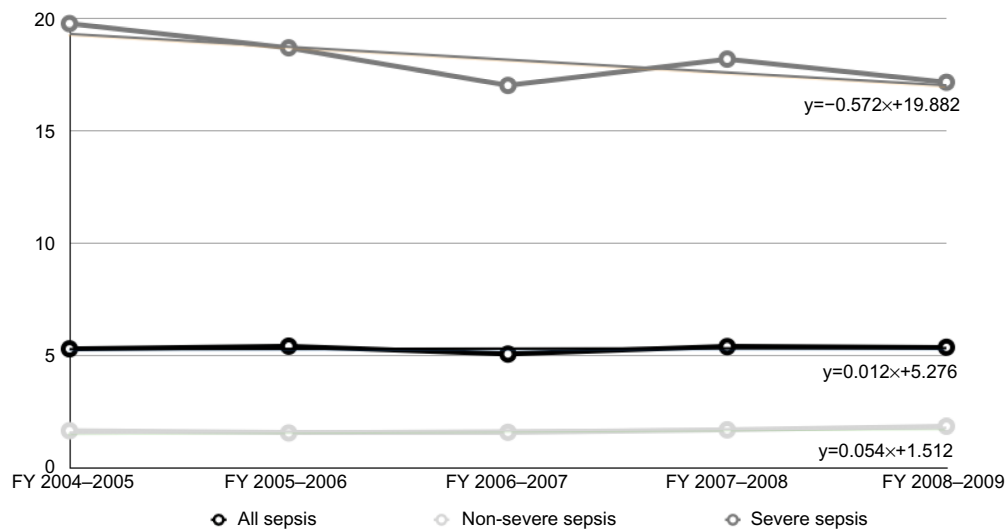


Figure 3 Crude sepsis mortality rates for hospitalized Canadian children by severity. **Abbreviation:** FY, fiscal year.

Organ failure commonly occurs in children with severe sepsis. In our cohort, respiratory failure occurred most frequently (81%). Angus et al²¹ also demonstrated higher rates of mortality amongst adults with respiratory failure (46%), although their numbers may be lower due to using a sample including all age spectrums. While very common in children with severe sepsis, the mortality rate in children with respiratory failure is fortunately less than 20%. This is in comparison to children with hepatic or central nervous system failure, where mortality rates reach 50%; this may be explained by a potential neuro-mediated suppression of killer cells residing in the liver, leading to increased susceptibility to overwhelm-

ing disease leading to death. In addition, the number of organs failed was associated with odds of death.

During the study period, we found a significant decline in all-sepsis hospitalization rates over time. The introduction of pneumococcal and meningococcal vaccines into routine childhood immunization schedules has resulted in a significant decline in invasive disease attributed to these pathogens, which may be reflected in our reported rates of hospitalization. Across Canada, health care is governed by the Canada Health Act, though provincially administered; as a result, the timing of implementation of universal access to vaccines varies across the country. By 2006, conjugate

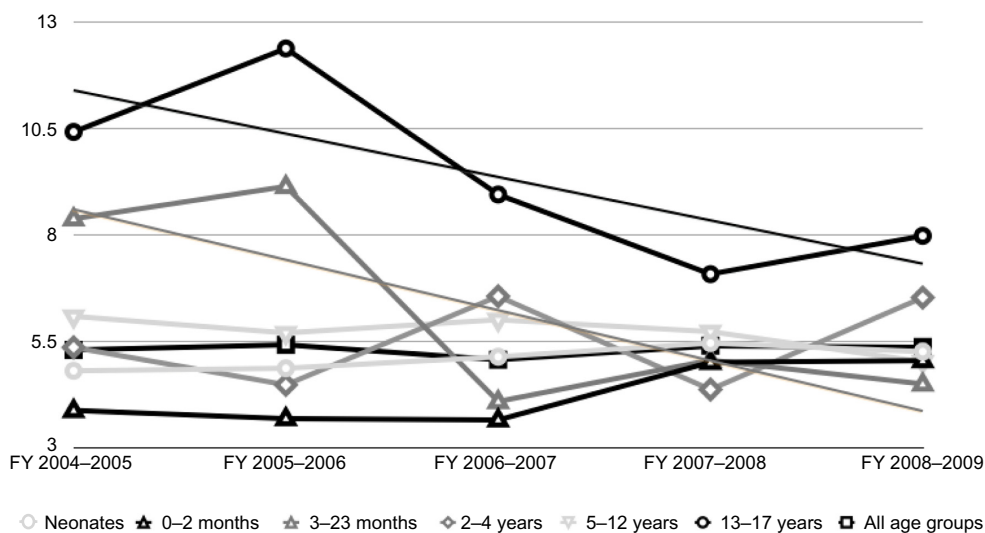


Figure 4 Crude sepsis mortality rates for hospitalized Canadian children by age. **Abbreviation:** FY, fiscal year.

Table 4 LOS in Canadian children hospitalized for sepsis between 2004 and 2009

	Mean LOS	Median LOS	Mean ICU LOS	Median ICU LOS
All sepsis	30.0	12.0	26.9	11.2
Severe sepsis	70.5	61.0	45.7	29.4
Non-severe sepsis	18.0	8.0	16.3	6.9

Abbreviations: ICU, intensive care unit; LOS, length of stay.

pneumococcal vaccine was available across all Canadian jurisdictions, while meningococcal vaccine programs were instituted between 2002 and 2007. This may also explain the significant decline in mortality over the study period in children aged 2–4 years who, during the study, received pneumococcal and meningococcal vaccine. Similarly, mortality in teens (13–17 years of age) declined, which is potentially related to meningococcal vaccine strategies.

Limitations

The use of a national-level administrative database may impart selection and reporting bias to the integrity of the results. ICD-10-CA coding is the current standard across Canada, with rigorous data quality assessment through the CIHI.^{25–32} The additional factor of voluntary reporting to the CIHI database may increase this bias. Furthermore, given the exclusion of data from the province of Quebec due to reporting differences, selection bias may increase. However, this analysis (without Quebec) represented approximately 76.7% of the Canadian population in 2008 (<http://www5.statcan.gc.ca/cansim/>), and to our knowledge, there is no difference between those children included and those who were not included in the CIHI database. To our knowledge, this is the largest known Canadian database related to sepsis and provides an overall national picture of recent trends related to hospitalization due to sepsis in Canadian children. However, the data presented are likely an underestimation as they are based on the use of administrative definitions only, rather than including a clinical definition based on sepsis being “any severe infection associated with organ dysfunction”. Additionally, sepsis episodes may be underreported having been coded using organ-specific infection instead of being classified as sepsis. Such limitations are inherent difficulties in determining the burden of sepsis globally.^{33–35} The definitions of sepsis, severe sepsis, and organ dysfunction based on the ICD-10-CA and CCI coding that were used in this study may not be consistent with those considered standard for pediatric sepsis in clinical studies.³⁶ They are, however, consistent with previous studies regarding sepsis that rely on administrative data.

Similarly, coding systems at different hospitals may vary, and a standard method for documenting interventions and outcomes is required to ensure accurate and reproducible epidemiologic data.³⁷ Given the nature of the secondary analysis of this study, the use of definitions from the original database reported by Husak et al⁵ was required.

Those children who presented to an emergency department (ED) with sepsis but died prior to hospital admission were not included in this analysis, as ED-specific data across the country were not available.

Conclusion

Sepsis remains an important cause of morbidity and mortality in Canadian children, posing a significant burden on health care resources. Age and sex continue to be associated with the incidence and severity of illness. Overall hospitalization rates have declined over time, as has mortality in severe sepsis. This report provides baseline metrics for future outcome-based research in Canada. Future research agendas may include targeting prevention strategies and early diagnosis as well as therapies preventing and managing organ failure.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Sepsis occurrence by diagnosis, ICD-10-CA codes

Diagnosis	FY 2004–2005		FY 2005–2006		FY 2006–2007		FY 2007–2008		FY 2008–2009	
	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Bacterial sepsis of newborn unspec (P369)	1,714	37.24	1,481	33.9	1,525	36.38	1,458	34.91	1,231	31.53
Septicemia unspec (A419)	688	14.95	599	13.71	580	13.84	566	13.55	541	13.86
Newborn sepsis due to oth/unspec staph (P363)	430	9.34	426	9.75	369	8.8	374	8.95	383	9.81
Other bacterial sepsis of newborn (P368)	171	3.72	152	3.48	195	4.65	219	5.24	243	6.22
Neonatal candidiasis (P375)	198	4.3	170	3.89	192	4.58	159	3.81	177	4.53
Septicemia due to <i>Escherichia coli</i> (A4150)	112	2.43	123	2.82	112	2.67	121	2.9	132	3.38
Sepsis of newborn due to <i>Escherichia coli</i> (P364)	104	2.26	95	2.17	96	2.29	112	2.68	123	3.15
Newborn sepsis due to <i>Streptococcus</i> group B (P360)	162	3.52	150	3.43	118	2.81	122	2.92	106	2.72
Septicemia due to other spec <i>Staphylococcus</i> (A411)	176	3.82	233	5.33	189	4.51	145	3.47	102	2.61
Septicemia due to <i>Streptococcus pneumoniae</i> (A403)	122	2.65	99	2.27	91	2.17	101	2.42	98	2.51
Other spec septicemia (A4188)	89	1.93	91	2.08	77	1.84	90	2.15	84	2.15
Septicemia due to <i>Staphylococcus aureus</i> (A410)	103	2.24	118	2.7	96	2.29	132	3.16	83	2.13
Septicemia due to other Gram-negative organisms (A4158)	45	0.98	55	1.26	41	0.98	72	1.72	77	1.97
Other streptococcal septicemia (A408)	50	1.09	64	1.46	54	1.29	62	1.48	75	1.92
Newborn sepsis due to <i>Staphylococcus aureus</i> (P362)	60	1.3	91	2.08	73	1.74	80	1.92	75	1.92
Newborn sepsis oth/unspec streptococci (P361)	70	1.52	55	1.26	69	1.65	75	1.8	69	1.77
Septicemia due to <i>Streptococcus</i> group A (A400)	21	0.46	45	1.03	38	0.91	35	0.84	45	1.15
Congenital herpes viral infection (P352)	22	0.48	23	0.53	26	0.62	23	0.55	38	0.97
Septicemia due to <i>Pseudomonas</i> (A4151)	22	0.48	35	0.8	21	0.5	23	0.55	37	0.95
Septicemia due to <i>Enterococcus</i> (A4180)	42	0.91	52	1.19	47	1.12	42	1.01	32	0.82
Candidal septicemia (B377)	43	0.93	49	1.12	29	0.69	23	0.55	26	0.67
Septicemia due to <i>Streptococcus</i> group B (A401)	32	0.7	29	0.66	31	0.74	30	0.72	23	0.59
Total	4,476	97.25	4,235	96.92	4,069	97.07	4,064	97.3	3,800	97.33

Note: Those diagnoses with <20 hospitalization episodes are not included.

Abbreviations: FY, fiscal year; ICD-10-CA, International Classification of Diseases and Related Health Problems, 10th Revision; oth, other; spec, specified; unspec, unspecified.

Table S2 ICD-10-CA and CCI coding for organ dysfunction

System	ICD-10-CA codes	CCI codes
Respiratory	J96.0, J96.9, J80, R09.2	I.GZ.31.CA-ND, I.GZ.31.CR-ND, I.GZ.31.GP-ND with extent attribute = "EX"
Cardiovascular	R57, I95.1, I95.8, I95.9	
Renal	N17	
Hepatic	K72.0, K72.9, K76.3	
Neurologic	F05.0, F05.9, G93.1, G93.4, G93.80	
Hematologic	D69.5, D69.6, D65	

Abbreviations: CCI, Canadian Classification of Health Interventions; ICD-10-CA, International Classification of Diseases and Related Health Problems, 10th Revision.

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