Sepsis ICD Coding Validation Study

Validation of ICD coding methods in estimating sepsis epidemiology: A prospective, observational cohort study

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CONFIDENTIAL

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95) annotated with Therapeutic goods Administration comments.

The George Institute for Global Health

1   Synopsis

Background: In 2017, The World Health Organization recognised sepsis as a global health priority.[1] However, estimation of true disease burden of sepsis remains difficult in lieu of lack of diagnostic tests and inconsistencies in the International Classification of Diseases (ICD) coding methodologies. We aim to use modification of IHME method to develop a reliable and reproducible estimate of the true sepsis burden in Australia using calibrated ICD coding methods.

Aim: To estimate the predictive value of sepsis ICD coding method using medical chart reviews and to compare the predictive values of modified-IHME and Angus ICD coding methods.

Study design: Prospective, observational, multicentre cohort study

Study population: Adult patients (aged 16 years old or more) admitted from the Emergency Department (ED) with an order of culture of any body fluid plus oral or intravenous administration of an antibiotic plus presence of ≥ 2 qSOFA score.

Methods: All ED admissions from 05 South West Sydney Local health District (SWSLHD) hospitals in NSW will be screened by a member of the research team to select 500 adult patients (aged 16 years old or more) using the study inclusion criteria. The two reviewers will review medical charts of the selected patients to determine if they meet the SEPSIS-3 criteria. The clinical diagnosis will be used to determine the predictive value of ICD coding. An analysis of initial 100 patients will be done to check if about 50% patients have clinical sepsis in the selected cohort and if required, inclusion criteria will be modified accordingly.

Data collection: Demographic and clinical characteristics of the selected cases will be recorded at the time of admission. At 96 hours after hospital admission, medical chart review will be done to identify clinical sepsis cases as per SEPSIS-3 criteria. For such cases the following additional information will be collected: onset of sepsis episode, site of infection, causative organism, time to antibiotic, type of organ dysfunction and presence of septic shock. On day 60 after hospital discharge, the assigned ICD codes and possibly death certificate data for patients who will die, will be obtained from the medical record department to apply Angus and modified-IHME methods.

Outcome: The findings from this study will provide valuable insights to calibrate ICD coding methods to give accurate and repeatable estimates of the burden of sepsis in SWSLHD in NSW which can be applied in other Australian states and territories and nationally.

2   Administrative Information

2.1   Investigator & participating Institutions

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Dr Paul M Middleton, Deputy Director, Emergency Medicine, Liverpool Hospital

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Dr Matthew Smith, Director of Emergency Medicine, Bankstown Hospital

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Note: More sites and site PIs may be added as necessary to achieve the study sample size

2.2   Study management committee

Dr Ashwani Kumar: Research Associate, PhD Candidate, Critical Care Division, The George Institute for Global Health, NSW, Australia

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3 General Information

3.1 Title
Validation of ICD coding methods in estimating sepsis epidemiology: A prospective, multi-centre cohort study.

3.2 Short Title
Sepsis ICD coding validation study.

4 Background and Rationale for Project

Sepsis is a major health problem and is associated with significant mortality and morbidity.[1-3] However, the burden of sepsis remains poorly understood both globally and in Australia, primarily because there is no definitive diagnostic test. As a result, use of administrative data such as ICD codes remains the only practical means to estimate sepsis epidemiology on a large scale.[4-7] ICD codes are the diagnostic classification standard proposed by WHO for all diseases disorders, injuries and other related health conditions for clinical and research purposes. These codes are assigned after a patient gets discharged from the hospital based on the primary and secondary diagnosis by designated hospital staff called Medical Coders. Several authors have used ICD coding methods to study the epidemiology of sepsis, amongst which Angus[8] and Martin[9] criteria are the most well-known and highly cited. However, currently there is no consensus regarding which ICD coding method should be used to define sepsis in administrative data and thereby estimate the true disease burden of sepsis.

The two predominant strategies to identify sepsis using ICD codes are 1) using specific ICD codes for sepsis, severe sepsis and septic shock, known as the 'explicit method' or 2) the presence of the ICD codes for infection and organ dysfunction during the same hospital episode, known as the "implicit" method. However, both strategies have some limitations. Explicit sepsis codes are only applied if sepsis or septic shock is documented in the clinical notes by the clinicians, which is not a common practice. The Implicit method comes with its own set of problems as various combination of infection and diagnosis codes have been proposed to identify sepsis, each suggesting different sepsis rates. Moreover, documentation of infection and organ dysfunction codes at discharge do not confirm if organ dysfunction was induced by infection or even existed at the same time during the hospital episode. Another issue is significant difference in the sepsis ICD coding practices, its documentation and selection of specific codes not just amongst different countries but within the same country or even same state. In a recent high-quality study in the USA using the Angus criteria, the explicit method underestimated sepsis incidence by approximately 50% whereas the implicit method overestimated incidence by 100%. These limitations result in estimates of the sepsis incidence varying up to four-fold depending on the method used.[10] Moreover, most previous

studies which estimated the predictive value of ICD coding were done using retrospective medical chart review. This design has an inherent limitation that information captured in the medical charts cannot be verified. Another common design is the analysis of administrative datasets which leverages the efficiency of large pre-existing data but is limited by variations in physician documentation and hospital coding practices.

Recently, the Institute for Health Metrics and Evaluation (IHME), an independent population health research centre at the University of Washington and WHO Global Burden of Disease (GBD) group, proposed a new ICD coding method to estimate the global sepsis disease burden. This method, which also classifies sepsis cases as Explicit or Implicit, differs from earlier estimates not only in its scope but also in using death certificate data, rather than hospitalization data.[11] However, it has not been prospectively validated. We aim to use modification of IHME method to develop a reliable and reproducible estimate of the burden of sepsis in SWSLHD in NSW, Australia by calibrating ICD coding of hospitalisation data using prospective medical chart review.

4.1 Aims and Objectives

4.1.1 Primary objectives

To estimate the predictive value of the modified IHME/GBD ICD coding method using prospective medical chart review.

4.1.2 Secondary objective

To compare the predictive value of modified IHME/GBD and Angus coding methods in estimating sepsis epidemiology.

5 Study Design

A prospective, observational, multicentre cohort study.

5.1 Inclusion criteria

-   Adult patients (aged 16 years old or more) admitted from the Emergency Department (ED) with an expected duration of hospital stay >24 hrs
-   An order of culture of body fluid plus oral or intravenous administration of an antibiotic
-   Presence of two of the following criteria (qSOFA score)
    o   Altered mental status (GCS <15)
    o   Respiratory rate $\geq$22/min
    o   Systolic blood pressure $\leq$100 mmHg

5.2 Data source

Data will be extracted from patient's clinical notes and medical records during the hospital stay.

5.3   Data collection

Demographic and clinical characteristics of the selected patients will be documented over their hospital admission period:

<u>At admission</u>

- MRN
- Age
- Sex
- qSOFA score
    - o   Respiratory rate
    - o   Systolic blood pressure
    - o   Glasgow Coma Score
- Baseline SOFA score, if available
- Order and/or culture of body fluid
- Order and/or administration of an antibiotic
- Co-morbidities

<u>Follow-up at 96 hours</u>

- ICU admission: Yes/No
- Total SOFA score

If total SOFA score is not documented in clinical notes, individual SOFA component scores will be calculated using SOFA worksheet (Appendix C).

For cases identified as having sepsis, following additional information will be collected:

- Date of sepsis episode
- Type of organ dysfunction
- Presence of septic shock
    - Use of a vasopressor to maintain Mean Arterial Pressure >65 mmHg, PLUS
    - Lactate > 2 mmol/dL (18 mg/dL)

<u>Day 60 (post admission)</u>

Following data will be obtained from the hospital medical record department (MRD):

- Assigned ICD codes
    - o   Primary diagnosis
    - o   Secondary diagnosis(es)
- Type of admission
    - o   Surgical
        - ▪   Elective
        - ▪   Emergency

       o   Medical
- Death Certificate data (for patients who will die)
- Time to antibiotic
- Site of infection
- Causative organism
- In-hospital LOS
- In-hospital mortality

Note: Patients who didn't meet clinical sepsis criteria at 96 hour follow up will be again evaluated at day 60 follow up if they met sepsis criteria between 96 hour and their discharge

If the same patient comes back to hospital during the study period, it will be considered as a separate admission.

6   Methods

All ED admissions from SouthWest Sydney Local Health District (SWSLHD) hospitals (Liverpool, Bankstown, Campbelltown, Bowral and Fairfield) in New South Wales will be screened by a member of the research team by applying the study inclusion criteria. Sites may choose to do the screening on 15-20 days in a month. More sites can be added, as required.

At 96 hrs after the admission, selected cases will be independently reviewed by two members of the research team to determine if they meet the clinical sepsis criteria. In case of disagreement between the two reviewers, the treating physician will be asked to make the judgement.

Clinical sepsis criteria (SEPSIS-3):

1. **Presumed serious infection:**
   - Order or documented administration of oral or parenteral antibiotics, PLUS
   - Order or documented sampling of body fluid cultures (blood, urine, cerebrospinal fluid, peritoneal, etc.) in a specified period#.

   #*If culture is obtained first, antibiotic must be administered within the next 72 hours, whereas if antibiotic is administered first, culture is required within the next 24 hours.*

   <div align="center">**AND**</div>

2. **Acute organ dysfunction**
   Infection-related increase in Sequential Organ Failure Assessment (SOFA) score of ≥ 2 from baseline

Note:
Baseline SOFA scores will be determined by the reviewer from the available data in the medical chart, estimating the degree of organ dysfunction prior to infection onset (if infection occurred during hospitalization) or at baseline health (if infection was present-on-admission). If no baseline SOFA score is available, then it should be assumed as '0'.

Last data collection will include principal and secondary diagnosis ICD codes along with some additional information which will be obtained from the MRD of each hospital. It will be determined by completion of coding which we expect to get completed by 60 days after

hospital discharge. Wherever possible, death certificate data will be collected for patients who will die.

Angus (Appendix A) and modified IHME/GBD (Appendix B) sepsis methods will be applied to identify database sepsis diagnosis.

Explicit sepsis cases will be those with an ICD code explicitly referencing sepsis (Appendix B.1) listed as a main cause of death or secondary admission diagnosis while implicit sepsis cases will be those with both an "infection code" listed as the underlying cause of death or primary admission diagnosis and an "organ dysfunction code" listed as a main cause of death or secondary admission diagnosis. If a case will meet criteria for both case definitions, it will be classified as explicit. Implicit sepsis cases will be identified using both Angus and modified-IHME criteria.

The predictive value of both ICD coding methods will be calculated using clinical diagnosis of sepsis as the gold standard.

Following table will be created for both Angus and modified-IHME ICD coding methods:

Database sepsis (n)	Clinical sepsis (n)	
	Yes	No
Yes	True Positive (TP)	False Positive (FP)
No	False Negative (FN)	True Negative (TN)

Predictive value parameters will be calculated as follows:

- Positive Predictive Value (PPV) = TP/(TP + FP) x 100
- Negative Predictive Value (NPV) = TN/(TN + FN) x 100
- Sensitivity = TP/TP+FN
- Specificity = TN/TN+FP

7   Safety Monitoring

As this is an observational study using data collected as part of routine clinical practice, no safety monitoring will be undertaken.

8   Statistical Analysis Plan

8.1   Sample size

Sample size calculation is based on considerations for the width of a two-sided 95% confidence interval (CI) of reported sensitivity of explicit sepsis ICD-10 codes between 7-16%.[12-14] For optimal statistical analysis, 50% of the enrolled patients should have the diagnosis of clinical sepsis in the selected patient cohort. For this reason and low incidence of sepsis in general population, inclusion criteria of presumed infection plus positive qSOFA will be used to select a patient's cohort with increased predicted risk of developing sepsis. A previous study in patients with diagnosed infection reported the proportion of Sepsis-3 positive cases as 32%[15] whereas a recently published Chinese study reported the sensitivity of qSOFA as 50.4% in predicting sepsis diagnosis in patients with infection.[16] Hence, we expect about 50% clinical sepsis cases (using SEPSIS-3 criteria) in our selected patient cohort and a sample size of 500 should provide about 250 cases of true sepsis cases. In lieu of limited

overall evidence and none from Australia on the predictive ability of our proposed eligibility criteria, we will conduct an initial analysis of first 100 patients to check the proportion of the clinical sepsis in our cohort. Based on the interim analysis results, study eligibility criteria will be modified, if required.

8.2   Data analysis

A descriptive analysis of the demographic and clinical characteristics will be presented. Continuous, normally distributed data will be presented as means with standard deviations (SDs), non-normally distributed data as medians with interquartile ranges (IQRs). Categorical data will be presented as numbers and proportions. Estimates of incidence will be presented with 95% confidence intervals (CIs).

9   Data Management

The principal means of data collection and data processing will be via online data entry performed by a member of the research team.

9.1   Site monitoring

No site monitoring will be performed.

9.2   Data recording and document retention

Each participating site will enter de-identified data into electronic CRF (eCRF). Each site will access the system through an individual password protected account and will only have access to their own site's data. Data will be stored in the Principal Investigator's office in electronic form on a database used specifically for the project.

All data collected by the study will be kept for a minimum of 7 years, or as otherwise required by regulatory authorities. Any paper data will be archived and stored in a secure facility.

9.3   Data quality assurance

Data entered by each site will be password-protected and the ability to access or change data prior to locking of the database will be restricted to that site and designated member of the research team. Once initial data collection has been completed, missing data and implausible values will be identified using predetermined objective criteria, and queries resolved through direct communication with sites if required. Treatment of outliers and missing data will be in accordance with a statistical analysis plan.

10   Outcome

The proposed study presents an opportunity to develop better ICD coding methods and to calibrate them using prospective clinical diagnosis to give an accurate and reproducible estimate of burden of sepsis in NSW, which can be applied to other Australian states and territories and nationally. Though, determining predictive ability of qSOFA for sepsis diagnosis is not a study objective, this study will provide additional valuable insights about the same as only a few studies have evaluated qSOFA as the predictor of sepsis diagnosis.

11 Funding

This study is currently being funded by internal sources from The George Institute for Global Health. Future funding will be sought via suitable grants.

12 Project Timeline

Anticipated timelines:

Date	Project Milestone
Jul 2019 – Jan 2020	Finalise Protocol
Nov 2019 – Mar 2020	Finalise list of participating hospitals in NSW
Feb 2020 – Jul 2020	Ethics submission & approval for participating hospitals
Jul - Nov 2020	Preparation of study documents, development of eCRF
Nov 2020 - Jan 2021	Expected enrolment start date
Jul 2022 – Sep 2022	Expected enrolment end date
Jan - Mar 2022	Data entry completed
Apr – Jun 2022	Data analysis
Jul - Nov 2022	Preparation of manuscript
Dec 2022 - Mar 2023	Presentation and publication of results

13 Ethical considerations

This is a low/negligible risk observational study as it is completely non-invasive in that it uses demographic, physiological and patient stay data which is measured routinely as part of clinical care. There is no change in the use of these data, nor is there data collected which is extra to that used in routine patient assessment and management. There are no interventions in the study and patient management will not be influenced in any way. Gaining informed consent in the ED setting has been the subject of much debate, and in the circumstances of observational nature of this study, the risk to the individual patient is extremely low, and essentially translates to those risks surrounding privacy principles. The NHMRC National Statement (section 2.3.6 (a)) requires that the research 'carries no more than low risk' and that the 'only foreseeable risk is one of discomfort'.

Alternatives to prospective informed consent include proxy consent, a waiver from individual participant consent and retrospective or deferred consent. There is evidence in proxy consent that the proxy may demonstrate poor agreement with the wishes of the participant; also, proxy consent may not be available in the timely manner necessary for interventions with a narrow therapeutic window. Deferred consent is used when it is not possible to obtain prospective informed consent from the participant or proxy, and consent is obtained from the participant as soon as is feasible after the intervention. However, not only does deferred consent run the risk of loss to follow up of patients enrolled in the study, but particularly in the emergency setting also involves attempts to contact the patient after discharge, a process which may cause unnecessary psychological distress and anxiety. A waiver of individual consent has been suggested as a solution to many 'low-risk' investigations in emergency

medicine, allowing consideration of factors such as minimal or no risk to the patient or staff, and the mandate to produce sound research-based evidence for time-critical interventions.

In the current study, there is no clinical risk associated for participants as the study is observational in nature and has no potential to interfere with standard treatment. There is no risk to the rights, privacy or professional reputation of carers, health professionals and/or institutions as the study solely concerns with analysis of clinical data collected as part of standard clinical care. Moreover, there won't be any clinical interaction between study participants and the research team as data will be captured from patients' clinical notes and medical records. Given the observational nature of the study and no perceived risks to patient health or safety, ethical approval will be sought with a waiver of consent.

14 Regulatory Requirements

This study will be conducted in accordance with the ICH and GCP principles.

15 Publication Policy

Data collected in the study will be presented at Intensive care conferences and other forums as appropriate. Data will subsequently be used for scientific publications in academic journals. It may also provide support for research applications.

16 Trial Registration

ANZCTR registration no. ACTRN12621000333819.

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18 Appendices

Appendix A: Angus Sepsis Definition

ICD-10-AM translation of infection codes used by Angus et al[13]	
A00 Cholera	A51 Early syphilis
A01 Typhoid and paratyphoid fevers	A52 Late syphilis
A02 Other salmonella infections	A53 Other and unspecified syphilis
A03 Shigellosis	A54 Gonococcal infection
A04 Other bacterial intestinal infections	A65 Nonvenereal syphilis
A05 Other bacterial food-borne intoxications	A66 Yaws
A08 Viral and other specified intestinal infections	A67 Pinta (carate)
A09 Diarrhea and gastroenteritis, presumed infectious origin	A69 Other spirochetal infections
A15 Respiratory tuberculosis, bacteriologically and histologically confirmed	B35 Dermatophytosis
	B36 Other superficial mycoses
A16 Respiratory tuberculosis, confirmed bacteriologically or histologically	B37 Candidiasis
	B38 Coccidioidomycosis
A17 Tuberculosis of nervous system	B39 Histoplasmosis
A18 Tuberculosis of other organs	B40 Blastomycosis
A19 Miliary tuberculosis	B41 Paracoccidioidomycosis
A20 Plague	B42 Sporotrichosis
A21 Tularemia	B43 Chromomycosis and phaeomycotic abscess
A22 Anthrax	B44 Aspergillosis
A23 Brucellosis	B45 Cryptococcosis
A24 Glanders and melioidosis	B46 Zygomycosis
A25 Rat-bite fevers	B47 Mycetoma
A27 Leptospirosis	B48 Other mycoses, not elsewhere classified
A28 Other zoonotic bacterial diseases, not elsewhere classified	B49 Unspecified mycosis
A30 Leprosy (Hansen's disease)	G00 Bacterial meningitis, not elsewhere classified
A31 Infection due to other mycobacteria	G01 Meningitis in bacterial diseases classified elsewhere
A32 Listeriosis	G02 Meningitis in other infectious and parasitic diseases classified elsewhere
A33 Tetanus neonatorum	
A34 Obstetrical tetanus	G03 Meningitis due to other and unspecified causes
A35 Other tetanus	G04 Encephalitis, myelitis and encephalomyelitis
A36 Diphtheria	G05 Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
A37 Whooping cough	
A38 Scarlet fever	G06 Intracranial and intraspinal abscess and granuloma
A39 Meningococcal infection	G07 Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere
A40 Streptococcal sepsis	
A41 Other sepsis	G08 Intracranial and intraspinal phlebitis and thrombophlebitis
A42 Actinomycosis	G09 Sequelae of inflammatory diseases of central nervous system
A43 Nocardiosis	
A44 Bartonellosis	I30 Acute pericarditis
A46 Erysipelas	I33 Acute and subacute endocarditis
A48 Other bacterial diseases, elsewhere classified	I80 Phlebitis and thrombophlebitis
A50 Congenital syphilis	J01 Acute sinusitis
A49 Bacterial infection of unspecified site	J02 Acute pharyngitis

J03 Acute tonsillitis

J04 Acute laryngitis and tracheitis

J05 Acute obstructive laryngitis (croup) and epiglottitis

J06 Acute upper respiratory infections of multiple and unspecified sites

J13 Pneumonia due to *Streptococcus pneumoniae*

J14 Pneumonia due to *Haemophilus influenzae*

J15 Bacterial pneumonia, not elsewhere classified

J16 Pneumonia due to other infectious organisms, not elsewhere classified

J17 Pneumonia in diseases classified elsewhere

J18 Pneumonia, organism unspecified

J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection

J44.1 Chronic obstructive pulmonary disease with acute exacerbation, unspecified

J47 Bronchiectasis

J85 Abscess of lung and mediastinum

J86 Pyothorax

K35 Acute appendicitis

K36 Other appendicitis

K37 Unspecified appendicitis

K57.02 Diverticulitis of small intestine with perforation and abscess, no hemorrhage

K57.03 Diverticulitis of small intestine with perforation and abscess, hemorrhage

K57.12 Diverticulitis of small intestine without perforation and abscess, no hemorrhage

K57.13 Diverticulitis of small intestine without perforation and abscess, hemorrhage

K57.22 Diverticulitis of large intestine with perforation and abscess, no hemorrhage

K57.23 Diverticulitis of large intestine with perforation and abscess, hemorrhage

K57.32 Diverticulitis of large intestine without perforation and abscess, no hemorrhage

K57.33 Diverticulitis of large intestine without perforation and abscess, hemorrhage

K57.42 Diverticulitis of both small and large intestine with perforation and abscess, no hemorrhage

K57.43 Diverticulitis of both small and large intestine with perforation and abscess, hemorrhage

K57.52 Diverticulitis of both small and large intestine without perforation and abscess, no hemorrhage

K57.53 Diverticulitis of both small and large intestine without perforation and abscess, hemorrhage

K57.82 Diverticulitis of intestine, part unspecified, with perforation and abscess, no hemorrhage

K57.83 Diverticulitis of intestine, part unspecified, with perforation and abscess, hemorrhage

K57.92 Diverticulitis of intestine, part unspecified, without perforation or abscess, no hemorrhage

K57.93 Diverticulitis of intestine, part unspecified, without perforation or abscess, hemorrhage

K61 Abscess of anal and rectal regions

K65 Peritonitis

K63.0 Abscess of intestine

K63.1 Perforation of intestine (nontraumatic)

K75.0 Abscess of liver

K75.1 Phlebitis of portal vein

K81.0 Acute cholecystitis

N10 Acute tubulointerstitial nephritis

N11 Chronic tubulointerstitial nephritis

N12 Tubulointerstitial nephritis, not specified as acute or chronic

N34 Urethritis and urethral syndrome

N39.0 Urinary tract infection, site not specified

N41 Inflammatory diseases of prostate

N70 Salpingitis and oophoritis

N71 Inflammatory disease of uterus, except cervix

N72 Inflammatory disease of cervix uteri

N73 Other female pelvic inflammatory diseases

N74 Female pelvic inflammatory disorders in diseases classified elsewhere

N75 Diseases of Bartholin's gland

N76 Other inflammation of vagina and vulva

N77 Vulvovaginal ulceration and inflammation in diseases classified elsewhere

L03 Cellulitis

L04 Acute lymphadenitis

L08 Other local infections of skin and subcutaneous tissue

L88 Pyoderma gangrenosum

M00 Pyogenic arthritis

M86 Osteomyelitis

A49.9 Bacterial infection, unspecified

T82.6 Infection and inflammatory reaction due to cardiac valve prosthesis

T82.7 Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts T83.5 Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system

T83.6 Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract

T84.5 Infection and inflammatory reaction due to internal joint prosthesis

T84.6 Infection and inflammatory reaction due to internal fixation device

T84.7 Infection and inflammatory reaction due to other internal orthopedic prosthetic devices, implants and grafts

T85.7 Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts

T81.4 Infection following a procedure, not elsewhere classified

T88.0 Infection following immunization

ICD-10-AM translation of organ dysfunction codes used by Angus et al[13]

R57 Shock, not elsewhere classified	D69.6 Thrombocytopenia, unspecified
I95 Hypotension	D69.8 Other specified hemorrhage conditions
Block 569 Continuous ventilatory support	D69.9 Hemorrhagic condition, unspecified
G93.4 Encephalopathy, unspecified	D65 Disseminated intravascular coagulation (defibrination syndrome)
F05 Delirium, not induced by alcohol and other psychoactive Substances	K72.0 Acute and subacute hepatic failure
G93.1 Anoxic brain damage, not elsewhere classified	K76.3 Infarction of liver
D69.5 Secondary thrombocytopenia	N17 Acute renal failure

1. **Explicit criteria** (Presence of any one of the following ICD codes)

Sepsis-specific ICD-10 code

Appendix B: Modified IHME/GBD_ICD coding method to identify sepsis

A02.1 Salmonella sepsis

A20.7 Sepsis due to plague
A21.7 Sepsis due to tularemia
A22.7 Sepsis due to anthrax
A24.1 Sepsis due to melioidosis
A26.7 Sepsis due to erysipelothrix
A28.2 Sepsis due to extraintestinal yersiniosis
A32.7 Sepsis due to listeria monocytogenes
A39.4 Meningococcemia, unspecified
A40 Streptococcal sepsis
A41 Other sepsis

A42.7 Sepsis due to actinomyces
A54.86 Sepsis due to gonococcal infection
B00.7 Disseminated herpesviral disease
B37.7 Candidal sepsis
R57.2 Septic Shock
R65.1 Systemic Inflammatory Response Syndrome of infectious origin with organ failure
O85 Puerperal sepsis

Implicit criteria (Presence of one infection code plus one organ dysfunction code)

Infection-related ICD-10 codes

A00	Cholera
A01	Typhoid fever
A02	Other salmonella infections
A03	Shigellosis
A04	Other bacterial intestinal infections
A05	Other bacterial food-borne intoxications
A06	Amebiasis
A07	Other protozoal intestinal diseases
A08	Viral and other specified intestinal infections
A09	Diarrhea and gastroenteritis, presumed infectious origin
A19	Miliary tuberculosis
A20	Plague
A21	Tularemia
A22	Anthrax
A23	Brucellosis
A24	Glanders and melioidosis
A25	Rat-bite fevers
A26	Erysipeloid
A27	Leptospirosis
A28	Other zoonotic bacterial diseases, not elsewhere classified
A30	Leprosy
A31	Infection due to other mycobacteria
A32	Listeriosis
A36	Diphtheria
A37	Whooping cough
A38	Scarlet fever
A39.0	Meningococcal meningitis
A39.1	Waterhouse-Friderichsen syndrome
A39.2	Acute meningococcemia
A39.3	Chronic meningococcemia
A39.4	Meningococcemia, unspecified
A39.5	Meningococcal heart disease
A39.81	Meningococcal encephalitis
A39.82	Meningococcal retrobulbar neuritis
A39.89	Other meningococcal infections
A39.9	Meningococcal infection, unspecified
A42	Actinomycosis
A43	Nocardiosis
A44	Bartonellosis
A46	Erysipelas
A48	Other bacterial diseases, elsewhere classified
A48.0	Gas gangrene
A48.1	Legionnaires disease
A48.3	Toxic shock syndrome
A49	Bacterial infection of unspecified site
A49.9	Bacterial infection, unspecified
A54	Gonococcal infection
A59	Trichomoniasis
A69.0	Necrotising ulcerative stomatitis
A69.1	Other Vincent's infections
A69.9	Spirochetal infection, unspecified
A70	Chlamydia psittaci infections
A74	Other diseases caused by chlamydiae
A75	Typhus fever

A77	Spotted fever (tick-borne rickettsioses)
A78	Q fever
A79	Other rickettsioses
A80	Acute poliomyelitis
A81	Atypical virus infections of CNS
A83	Mosquito-borne viral encephalitis
A84	Tick-borne viral encephalitis
A85	Other viral encephalitis, not elsewhere classified
A86	Unspecified viral encephalitis
A87	Viral meningitis
A88	Other viral infections of CNS, not elsewhere classified
A89	Unspecified viral infection of CNS
A90	Dengue fever
A91	Dengue hemorrhagic fever
A92	Other mosquito-borne viral fevers
A93	Other arthropod-borne viral fevers, not elsewhere classified
A94	Unspecified arthropod-borne viral fever
A95	Yellow fever
A96	Arenaviral hemorrhagic fever
A98	Other viral hemorrhagic fever, not elsewhere classified
A99	Unspecified viral hemorrhagic fever
B00	Herpesviral [herpes simplex] infections
B01	Varicella
B02	Zoster
B03	Smallpox
B04	Moneypox
B05	Measles
B06	Rubella
B08	Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified
B09	Unspecified viral infection characterized by skin and mucous membrane lesions
B10	Other human herpesviruses
B25	Cytomegaloviral disease
B26	Mumps
B27	Infectious mononucleosis
B33	Other viral diseases, not elsewhere classified
B34	Viral infection of unspecified site
B37	Candidiasis
B38	Coccidioidomycosis
B38.7	Disseminated coccidioidomycosis
B39	Histoplasmosis
B39.3	Disseminated histoplasmosis capsulati
B40	Blastomycosis
B40.7	Disseminated blastomycosis
B41	Paracoccidioidomycosis
B41.7	Disseminated paracoccidioidomycosis
B42	Sporotrichosis
B42.7	Disseminated sporotrichosis
B43	Chromomycosis and phaeomycotic abscess
B44	Aspergillosis
B44.7	Disseminated aspergillosis
B45	Cryptococcosis
B45.7	Disseminated cryptococcosis

B46	Zygomycosis
B46.4	Disseminated mucormycosis
B48	Other mycoses, not elsewhere classified
B49	Unspecified mycosis
B50	Pasmodium falciparum malaria
B50.8	Other severe and complicated Plasmodium falciparum malaria
B54	Unspecified malaria
B55	Leishmaniasis
B57	Chagas Disease
B58	Toxoplasmosis
B59	Pneumocystosis
B60	Other protozoal diseases, not elsewhere classified
B64	Unspecified protozoal disease
B67	Echinococcosis
B95	Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere
B96	Other bacterial agents as the cause of diseases classified elsewhere
B97	Viral agents as the cause of diseases classified elsewhere
B99	Other and unspecified infectious diseases
G00	Bacterial meningitis, not elsewhere classified
G01	Meningitis in bacterial diseases classified elsewhere
G02	Meningitis in other infectious and parasitic diseases classified elsewhere
G03	Meningitis due to other and unspecified causes
G04	Encephalitis, myelitis and encephalomyelitis
G05	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
G06	Intracranial and intraspinal abscess and granuloma
G07	Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere
G08	Intracranial and intraspinal phlebitis and thrombophlebitis
H05.01	Cellulitis of orbit
H05.02	Osteomyelitis of orbit
H05.03	Periostitis of orbit
H60.2	Malignant otitis externa
H70.0	Acute mastoiditis
I00	Rheumatic fever without heart involvement
I26.01	Septic pulmonary embolsim with acute cor pulmonale
I26.90	Septic pulmonary embolism without acute cor pulmonale
I33	Acute and subacute endocarditis
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40.0	Infective myocarditis
I76	Septic non-pulmonary arterial embolism
I96	Gangrene, not elsewhere classified
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis (croup) and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J09	Influenza due to certain identified influenza viruses
J10	Influenza due to other identified influenza virus
J11	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J36	Peritonsillar abscess
J39.0	Retropharyngeal and parapharyngeal abscess
J39.1	Other abscess of pharynx
J85	Abscess of lung and mediastinum
J86	Pyothorax
K35	Acute appendicitis
K36	Other appendicitis
K37	Unspecified appendicitis
K57	Diverticulitis disease of intestine
K61	Abscess of anal and rectal regions
K63.0	Abscess of intestine
K63.1	Perforation of intestine (nontraumatic)
K65	Peritonitis
K75.0	Abscess of liver
K81.0	Acute cholecystitis
K81.2	Acute cholecystitis with chronic cholecystitis
K83.0	Cholangitis
K95.01	Infection due to gastric band procedure
K95.81	Infection due to other bariatric procedure
L02	Cutaneous abscess, furuncle and carbuncle
L03	Cellulitis
L04	Acute lymphadenitis
L08	Other local infections of skin and subcutaneous tissue
M00	Pyogenic arthritis
M01	Direction infections of joint in infectious and parasitic diseases classified elsewhere
M86	Osteomyelitis
N10	Acute pyelonephritis
N15.1	Renal and perinephric abscess
N30	cystitis
N39.0	Urinary tract infection, site not specified
N41.0	Acute prostatitis
N41.2	Abscess of prostate
N41.3	Prostatocystitis
N45	Orchitis and epididymitis
N70	Salpingitis and oophoritis
N71	Inflammatory disease of uterus, except cervix
N72	Inflammatory disease of cervix uteri
N73	Other female pelvic inflammatory diseases
N74	Female pelvic inflammatory disorders in diseases classified elsewhere
N98.0	Infection associated with artificial insemination
O03.0	Genital tract and pelvic infection following incomplete spontaneous abortion
O03.5	Genital tract and pelvic infection following complete or unspecified spontaneous abortion
O03.88	Urinary tract infection following complete or unspecified spontaneous abortion
O04.5	Genital tract and pelvic infection following (induced) termination of pregnancy
O04.88	Urinary tract infection following (induced) termination of pregnancy
O07.38	Urinary tract infection following failed attempted termination of pregnancy
O08.0	Genital tract and pelvic infection following ectopic and molar pregnancy
O08.83	Urinary tract infection following ectopic and molar pregnancy
O23	Infections of genitourinary tract in pregnancy
O75.3	Other infection during labour
O86	Other puerperal infections
O88.3	Obstetric pyemic and septic embolism
O91	Infections of breast associated with pregnancy, the puerperium and lactation
O98	Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium
R78.81	Bacteraemia NOS

T80.2   Sepsis following infusion, transfusion, or therapeutic injection

T81.4   Infection following a procedure, not elsewhere classified

T82.6   Infection and inflammatory reaction due to cardiac valve prosthesis

T82.7   Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts

T83.5   Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system

T83.6   Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract

T84.5   Infection and inflammatory reaction due to internal joint prosthesis

T84.6   Infection and inflammatory reaction due to internal fixation device

T84.7   Infection and inflammatory reaction due to other internal orthopedic prosthetic devices, implants and grafts

T85.7   Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts

T88.0   Sepsis following immunization

U04   Severe Acute Respiratory Syndrome (SARS)

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2.   Organ Dysfunction Codes

D65   Disseminated intravascular coagulation [defibrination syndrome]

D69.5   Secondary thrombocytopenia

E87.2   Acidosis

G93.4   Other and unspecified encephalopathy

I46   Cardiac arrest

I95.9   Hypotension, unspecified

J80   Acute respiratory distress syndrome

J95.2   Acute pulmonary insufficiency following nonthoracic surgery

J96   Respiratory failure, not elsewhere classified

J96.0   Acute respiratory failure

J96.2   Acute and chronic respiratory failure

J96.9   Respiratory failure, unspecified

K72.0   Acute and subacute hepatic failure

K72.9   Hepatic failure, unspecified

N00   Acute nephritic syndrome

N17   Acute kidney failure

R09.02   Hypoxemia

R09.2   Respiratory arrest

R40.0   Somnolence

R40.1   Stupor

R40.2   Coma

R40.20   Unspecified coma

R41.82   Altered mental status, unspecified

R55   Syncope and collapse

R57   Shock, not elsewhere classified

Appendix C: SOFA calculation worksheet

ORGAN SYSTEM	0	1	2	3	4	9	Organ scores
Respiration							
PaO₂ / FIO₂							
(in mmHg)	>400	301 - 400	201 – 300 (with respiratory support*) <301 (without respiratory support*)	101 - 200 (with respiratory support*)	≤ 100 (with respiratory support*)	Variable not measured	
(in kPa)	>53.2	40.0 – 53.1	26.7 – 39.9 (with respiratory support*) <40.0 (without respiratory support*)	13.4 – 26.6 (with respiratory support*)	≤ 13.3 (with respiratory support*)		
Cardiovascular							
Hypotension	MAP > 70 mmHg	MAP < 70 mmHg	dopamine ≤ 5.0 (doses are given in µg / kg / minute) or any dose dobutamine or any dose milrinone or any dose levosimendan	dopamine 5.0 – 15.0 (doses are given in µg / kg / minute) or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 or any dose vasopressin or any dose metaraminol or any dose phenylephrine	dopamine > 15.0 (doses are given in µg / kg / minute) or epinephrine >0.1 or norepinephrine >0.1	Variable not measured	
Coagulation							
Platelets (x 10⁹ / L)	>150	101 - 150	51 - 100	21 - 50	≤ 20	Variable not measured	
Liver							
Bilirubin							
(mg / dl)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12.0	Variable not measured	
(µmol / L)	<20	20 - 32	33 - 101	102 - 204	>204		
Renal							
Creatinine							
(mg / dl)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	> 5.0	Variable not measured	
(µmol/l)	< 110	110 – 170	171 – 299	300 – 440	> 440		
OR Urine output				or < 500 ml / day	or < 200 ml / day		
Central Nervous System (GCS)							
	15	13-14	10-12	6-9	<6		