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Sepsis survivorship

A review of the impacts of surviving sepsis for Australian patients

Kelly Shaw from KP Health, Melbourne, Australia, prepared this report on behalf of the Australian Commission on Safety and Quality in Health Care.

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Preface

The Australian Commission on Safety and Quality in Health Care (the Commission) has commenced a program of work to improve early recognition, treatment and outcomes for patients with sepsis in Australia.

In consultation with internal and external stakeholders, the Commission has identified a series of actions that will be implemented over 2020–22. The program of work to improve outcomes in patients with sepsis in Australia includes:

- Performing an epidemiological analysis of national inpatient sepsis data
- Conducting a retrospective medical record review of records belonging to patients with sepsis; the findings from the audit could inform the development of sepsis coding
- Conducting a literature review of trigger tools that promote the early detection of sepsis symptoms
- Developing materials relevant to Standard 3 and Standard 8 of the National Safety and Quality Health Service (NSQHS) Standards (2nd edition) to ensure health service organisations demonstrate the use of evidence-based practice in the early detection, treatment and monitoring of sepsis
- Revising the *Antimicrobial Stewardship Clinical Care Standard* to strengthen Quality Statement 1 with regard to the role that prompt treatment with intravenous antibiotics has in preventing sepsis in patients who have a suspected severe infection
- Developing national clinical guidance materials to support improvements in the delivery of sepsis care
- Partnering with the Australian Government, states and territories and the George Institute for Global Health to lead a multi-modal public awareness campaign
- Scoping the need to establish a coordinated approach to improving services to address the high rates of disease recurrence and associated morbidity and disability (this report).

Aim

This literature review was commissioned to describe the evidence regarding the burden of disease associated with sepsis in the Australian population and the impacts of sepsis on people who survive. Evidence for interventions to improve recovery and reduce sepsis morbidity are also described.

Review questions

The review addresses the following research questions:

1. How many people survive sepsis each year by age and by sex in Australia?
2. Does Australia have better or worse outcomes for people who survive sepsis by age and sex than countries with similar health systems?
3. What complications do survivors of sepsis face after discharge from hospital?
4. How frequently are survivors readmitted to hospital in that period?
5. What interventions improve recovery after discharge and reduce ongoing morbidity?
    a. How have these interventions been evaluated and which ones were successful?
    b. What measures were used to demonstrate success?
    c. Which of these interventions could work in the Australian context?

Overview of findings

The authors identified 32 publications of broad relevance to the review: one guideline, 19 systematic reviews, two randomised controlled trials, five observational studies, two qualitative studies, two data linkage analyses and one burden of disease study.

The key findings of this review were:

- The number of Australians who survive sepsis each year is largely unknown
- Available evidence suggests Australia has a lower incidence of sepsis and lower 30-day septic shock mortality compared with North America and Europe
- Sepsis diagnosis is associated with increased premature mortality in adults
- People who survive sepsis are at increased risk of subsequent premature mortality, recurrent infection, impaired cognitive or physical function and reduced quality of life; one in five people will be re-admitted to hospital within 30 days of hospital discharge after sepsis
- People who survive sepsis may experience cognitive impairment; this has been observed in adults and children after sepsis; children and neonates may also experience neurodevelopmental impacts, vision and hearing impairment
- There are few studies that have explored interventions to improve recovery after hospital discharge and to reduce ongoing morbidity after sepsis
- Available evidence indicates sepsis patients, their families and caregivers require information about their diagnosis, prognosis and where they can receive support for their ongoing care needs
- Some people need assistance navigating the health system to access the follow-up care they require after treatment for sepsis
- Caregivers report an increased caring burden for patients following sepsis and may need access to additional services and resources to provide support.

There is very little evidence for interventions to improve mortality, morbidity and quality of life in patients after sepsis. The authors found one study that searched for but did not find evidence for rehabilitation interventions after hospital discharge. Another study assessed a primary care intervention, which had little impact on patient goals and wishes. Studies of specialised nurse-led intensive care unit follow-up clinics, exercise programs and case management interventions have shown small and inconsistent benefits.

An International Sepsis Forum colloquium in 2018 identified important research gaps and concluded there are few studies of in-hospital or post-hospital interventions to enhance longer-term survival and quality of life.

There is a need for research to identify interventions to improve survival, quality of life and cognitive and physical function in people who have survived sepsis.

Conclusion and next steps for the Commission

This review demonstrated that there is very little evidence for specific interventions – developed, trialled or implemented – to improve mortality, morbidity or quality of life in patients after hospital discharge for sepsis. Opportunities exist to address knowledge gaps and improve post-hospital discharge sepsis support services. This includes conducting research to identify effective strategies that improve survival, quality of life and cognitive and physical function in people who have survived sepsis.

To better understand the key contributing factors relating to an overall absence of survivorship services for sepsis patients, the Commission will:

- Conduct further qualitative research with survivors of sepsis, building on the evidence and future opportunities outlined in this report.
- Review the findings from the report with the key stakeholders to identify where services or resources may be directed to better support survivors of sepsis in Australia.

Sepsis survivorship: A review of effective support strategies

Prepared for the Australian Commission on Safety and Quality in Health Care
February 2021

knowledge into practice

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Contents

Figures

Tables

Executive summary

Sepsis is a systemic inflammatory response syndrome to infection. Cases of sepsis are increasing among Australian hospital inpatients despite significant national progress to improve early detection, recognition and treatment of sepsis. Sepsis contributes to considerable morbidity and mortality among Australian hospital inpatients.

This literature review describes the burden of disease associated with sepsis in the Australian population and the impacts on people who survive sepsis. Evidence for interventions to improve recovery and reduce sepsis morbidity is also described.

We identified 32 publications of broad relevance to the review: one guideline, 19 systematic reviews, two randomised controlled trials, five observational studies, two qualitative studies, two data linkage analyses and one burden of disease study.

The number of Australians who survive sepsis each year is unknown. Estimates suggest in Australia there are over 48,000 hospital admissions each year where sepsis is the main reason for admission and approximately 1,400 deaths each year where the underlying cause of death is sepsis. Hospital admissions and deaths due to sepsis are increasing over time.

Australia has a lower incidence of sepsis and lower 30-day septic shock mortality compared with North America and Europe. There are few other data that are available to compare outcomes from sepsis in Australia with other countries.

People who survive sepsis are at increased risk of subsequent premature mortality, recurrent infection, impaired cognitive and or physical function and reduced quality of life. One in five people will be re-admitted to hospital within 30 days of hospital discharge after sepsis.

Most studies show sepsis diagnosis is associated with increased premature mortality in adults. However, mortality rates vary widely between studies. There are no long-term data available that estimate premature mortality in children and neonates who survive sepsis. Risk factors for mortality include older age, male sex, chronic disease comorbidities and tobacco use.

People who survive sepsis may experience cognitive impairment. This has been observed in adults and children after sepsis. Children and neonates may also experience neurodevelopmental impacts, visual and hearing impairment.

The impacts of sepsis on physical function include reduced physical fitness, conditioning and function, all of which contribute to loss of independence and autonomy in affected survivors. Other general physical symptoms have also been reported by patients.

Sepsis is associated with poorer quality of life in the immediate post-discharge period. This generally improves over time. However, some patients are left with residual quality of life impacts.

There are few studies that have explored interventions to improve recovery after hospital discharge and to reduce ongoing morbidity after sepsis. Available evidence indicates patients, their families and caregivers require information about their diagnosis, prognosis and where they can receive support for their ongoing care needs. Some people need assistance navigating the health system to access the follow-up care they require. Caregivers report an increased caring burden and may need additional support.

There is very little evidence for interventions to improve mortality, morbidity and quality of life in patients after sepsis. We found one study that searched for but did not find evidence for rehabilitation interventions after hospital discharge. Another study assessed a primary care intervention, which had little impact on patient goals and wishes. Studies of specialised nurse-led intensive care unit follow-up clinics, exercise programs and case management interventions have shown small and inconsistent benefits.

An International Sepsis Forum colloquium in 2018 identified important research gaps and concluded there are few studies of in-hospital or post-hospital interventions to enhance longer-term survival and quality of life.

There is a need for research to identify interventions to improve survival, quality of life and cognitive and physical function in people who have survived sepsis.

Background

The Australian Commission on Safety and Quality in Health Care (the Commission) is working to improve the experience and outcomes of people who experience sepsis in Australia. This review will inform the Commission's program of work.

The review was conducted to describe available evidence for effective strategies that address the high rates of disease recurrence and associated morbidity and disability after a person recovers from sepsis.

A review protocol was developed and approved by the Commission to agree on the review methodology.

Review questions

This review addresses the following research questions:

1. How many people survive sepsis each year by age and by sex in Australia?
2. Does Australia have better or worse outcomes for people who survive sepsis by age and sex than countries with similar health systems?
3. What complications do survivors of sepsis face after discharge from hospital?
4. How frequently are survivors readmitted to hospital?
5. What interventions improve recovery after discharge and reduce ongoing morbidity?
    a. How have these interventions been evaluated and which ones were successful?
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    c. Which of these interventions could work in the Australian context?

Review methods

We conducted a comprehensive review of the peer-reviewed literature and searched websites and grey literature to identify materials of broad relevance to the review questions.

We searched the peer-reviewed and grey literature using Medical Subject Heading (MeSH) terms and keywords of broad relevance as follows:

- To identify peer-reviewed publications we searched for articles published in English in the five years to 2020. The date of last search was 7 June 2020.
- To identify grey literature of relevance to sepsis survivorship, we used MeSH and keywords. The date of last search was 2 July 2020.

We interrogated the following databases and grey literature sources:

- Medline (via OVID)
- EMBASE
- CINAHL
- Cochrane Library
- PEDro
- Australian Clinical Practice Guidelines Portal
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- Canadian Medical Association InfoBase
- US National Guideline Clearinghouse
- New Zealand Ministry of Health Guides and Standards

- proprietary search engines (Google, Google Scholar, Edge)
- Commonwealth, State and Territory health department websites
- Australian Sepsis Network
- UK Sepsis Trust
- Global Sepsis Alliance
- Sepsis Alliance
- World Health Organization Sepsis Program
- International Sepsis Forum
- New Zealand Sepsis Trust

The search terms that were used to identify relevant studies in bibliographic databases (specific to Medline via Ovid) are described at Appendix A. Terms for each database were tailored to the requirements of each bibliographic database.

Inclusion and exclusion process

Guidelines

We considered all guidelines relevant to sepsis. We considered for inclusion any guidelines relevant to sepsis survivorship. That process included a review of evidence to support the development of the guideline.

We identified National Institute for Health and Care Excellence Sepsis Guidelines[1] that reported findings from evidence review of studies in sepsis survivors.

Systematic reviews and meta-analyses

We considered all systematic reviews and meta-analyses regardless of study design of included studies – quantitative or qualitative. Where there were two or more reviews that addressed the same question, we included all reviews that met inclusion criteria, but reporting focusses on the highest level of evidence and most recent search date.

We considered all systematic reviews and meta-analyses of sepsis survivorship and post-sepsis outcomes:

- Regardless of age or gender of participant
- With and without comparators
- Regardless of outcomes measures used.

Studies that did not report outcomes relevant to the review were not included. Studies in languages other than English were only included where a full-text translation into English was available.

Randomised controlled trials and observational studies

We considered all randomised controlled trials and observational studies that were not already considered for inclusion in an included systematic review if they described outcomes relevant to sepsis survivorship and post-sepsis outcomes. Studies in languages other than English were only included where a full-text translation into English was available.

Data extraction and quality appraisal

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database EndNote. Duplicates were removed, and all references were examined for their relevance. Full-text articles were sourced for all potentially eligible studies and these were assessed against the eligibility criteria. We tabulated reasons for exclusion for all articles that do not meet the criteria (Appendix B).

At the same time, we coded abstracts for relevant randomised controlled trials and observational studies that were identified in the searches. We retained these abstracts if the topic of the publication was sepsis survivorship. We considered these publications for inclusion if they were not already included in an included systematic review and were relevant to sepsis survivorship.

We extracted relevant data from included studies using a pre-defined template included in our review protocol.

We assessed the methodological quality of National Institute for Health and Care Excellence, UK (NICE) guidelines using the AGREE II (Appraisal of Guidelines for Research and Evaluation) quality appraisal tool.

We assessed the methodological quality of systematic reviews that met inclusion criteria using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) measurement tool. We applied AMSTAR assessment criteria to rate overall confidence in the results of each systematic review using methods outlined by Shea et al.[2] There are 16 questions in the AMSTAR 2 assessment tool. Of these, there are seven critical domains that describe critical methodological flaws that influence the quality of the review:

1. Protocol registered before commencement of the review.
2. Adequacy of the literature search
3. Justification for excluding individual studies
4. Risk of bias from individual studies being included in the review
5. Appropriateness of meta-analytical methods
6. Consideration of risk of bias when interpreting the results of the review
7. Assessment of presence and likely impact of publication bias.

Each included systematic review was assessed against the 16 items and seven critical domains and rated as follows:

- High – nil or one non-critical weakness
- Moderate – more than one non-critical weakness
- Low – one critical flaw with or without non-critical weaknesses
- Critically low – more than one critical flaw with or without non-critical weaknesses.

We assessed risk of bias of included randomised controlled trials using the Cochrane Risk of Bias tool. Bias is assessed as a judgement (high, low or unclear) for individual elements from five domains (selection, performance, attrition, reporting and ‘other’).

We assessed quality of non-randomised studies using the Newcastle–Ottawa Scale. Quality was assessed against three domains (selection, comparability and outcome/exposure). Each study was given a rating of good, fair or poor quality according to the following:

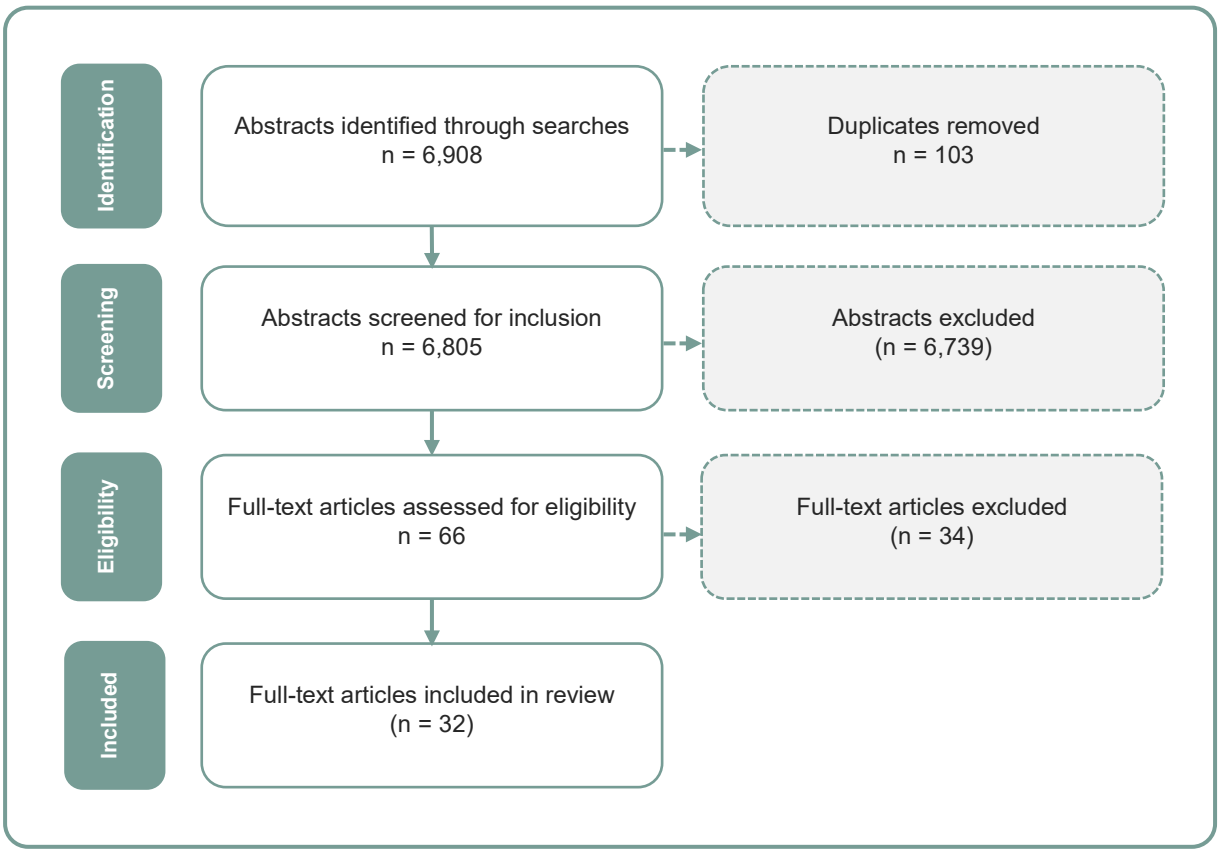
- Good – 3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain.

- Fair – 2 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain.
- Poor – 0 or 1 star in selection domain or 1 stars in comparability domain or 0 or 1 star in outcome/exposure domain.

Results

The results of our searches identified the following peer-reviewed materials of broad relevance to the review as shown in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement in Figure 1.

Figure 1: PRISMA Statement



Included publications

Included publications are summarised in Appendix C. We identified one relevant guideline, 19 systematic reviews, two randomised controlled trials and five observational studies. The randomised controlled trials and non-randomised studies were all published since 2018 and were not considered for inclusion in the included systematic reviews.

- The NICE guideline was rated as high-quality (7/7 AGREE II assessment).[1]
- One systematic review was rated as high-quality[3], three as moderate quality[4,5,6], nine as low-quality[7,8,9,10,11,12,13,14,15] and six as critically low-quality.[16,17,18,19,20,21] Given the paucity of available evidence, all systematic reviews were included in this review regardless of review quality.
- One RCT was rated as low risk of bias[22] and the other as high risk of bias.[23]
- Two non-randomised studies were rated as good quality[24,25], one as fair quality[26] and two as poor-quality.[27,28]

We identified an additional five publications of broad relevance to the review. One was the Global Burden of Disease Study (Sepsis)[29], two data linkage analyses[30,31], and two qualitative materials.[32,33]

Other materials

The following additional materials of importance in the Australian context were also identified through grey literature searches.

- Australian Bureau of Statistics. Causes of Death data
- Australian Institute of Health and Welfare. Hospital data cubes
- Australian and New Zealand Intensive Care Society (ANZICS) registry reports
- Australian Sepsis Network professional resources
- World Health Organization sepsis materials.

Limitation

The primary limitation to this literature review is the paucity of available evidence of effective strategies to reduce morbidity following a diagnosis of sepsis.

Question 1: How many people survive sepsis each year?

There are no data available that provide a precise estimate of how many people survive sepsis each year in Australia. This is a gap in our understanding of the epidemiology of sepsis both internationally and nationally. Available data are presented below and demonstrate that most patients with sepsis will survive their initial sepsis diagnosis.

Sepsis incidence

According to the World Health Organization (WHO) the global epidemiological burden of sepsis is difficult to ascertain and there are few measures that facilitate international comparisons.[34] The WHO estimates there could be 15–19 million cases of sepsis every year worldwide. These estimates are based exclusively on data from high-income countries.[34]

We included one systematic review of studies that estimate incidence of sepsis.[5] This systematic review of the literature measured variation in the incidence of community onset sepsis. A total of 14 observational studies (10 cohort, four case-control) were included in the review (see Appendix C). None were conducted in Australia.

The authors found wide variation in reported incidence of sepsis, largely due to differences in how sepsis was defined across studies. Nevertheless, the following estimates of the incidence of sepsis cases per 100,000 population per year are provided in Table 1:

Table 1: Estimated annual global incidence of sepsis

Type/stage of sepsis	Incidence per 100,000
Non-severe sepsis	64–514
Severe sepsis	40–455
Septic shock	9–31

If applied to the Australian context, crude estimates of annual caseload of sepsis in Australia would be as shown in Table 2:

Table 2: Estimated annual incidence of sepsis in Australia

Type/stage of sepsis	Incidence
Non-severe sepsis	16,000–128,400
Severe sepsis	10,000–114,000
Septic shock	2,250–7,750

The Global Burden of Disease Study (Sepsis) also provides population estimates of sepsis incidence.[29] This study derives sepsis incidence estimates by dividing estimated sepsis deaths by modelled in-hospital sepsis case fatality, which was established using individual-level hospital admission or discharge data. According to the results of this study as a basis, we estimate the age-standardised incidence of sepsis in Australia as 158.8 cases per 100,000 population per year. This is within the incidence range reported by Tsertsvadze in 2016.[5]

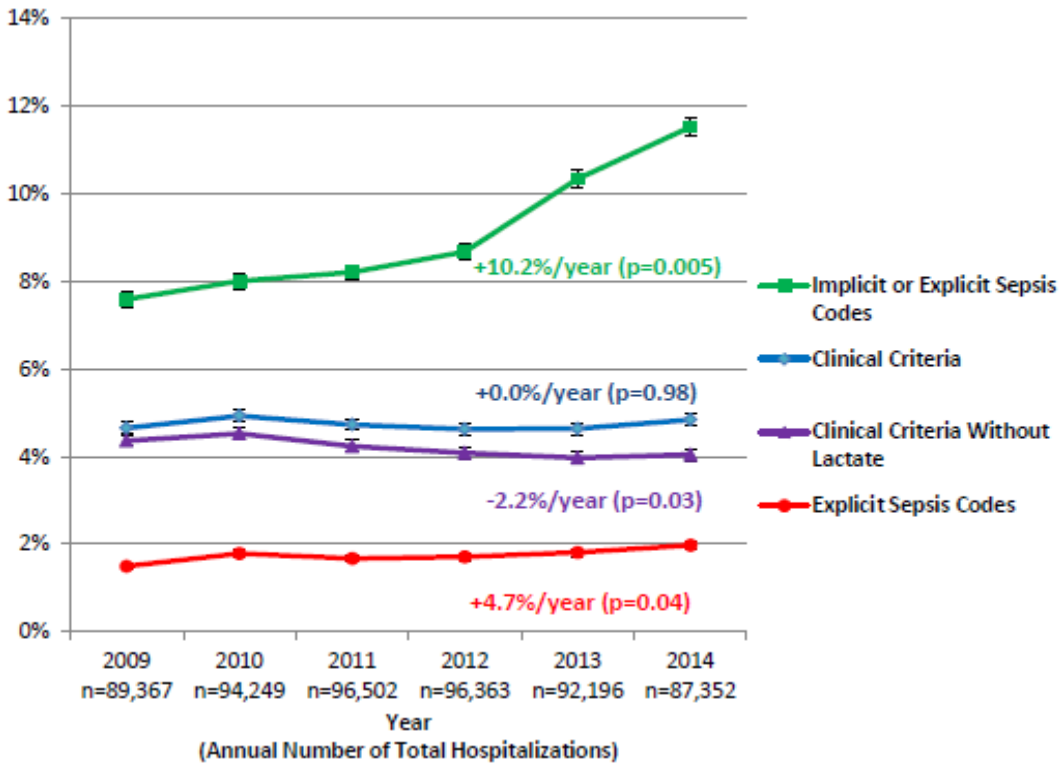
Sepsis hospitalisations

Survival in the subgroup of people who are hospitalised or require intensive care support can theoretically be estimated from available hospital administrative data collections, registry data and deaths data. However, coded administrative data have limitations too.

We included one systematic review[12] that described the relationship between International Classification of Diseases (ICD) coding and accurate sepsis diagnosis. The authors identified 12 studies conducted using health administration data. They demonstrated sepsis is largely under-coded in administrative data. They described issues associated with the validity of ICD-coded sepsis diagnosis codes when used in studies to identify patients with sepsis. A total of 38 sepsis case definitions were tested by the authors, including over 130 different ICD codes. Sensitivity ranged from 5.9% to 82.3%, specificity from 78.3% to 100%, positive predictive value ranged from 5.6% to 100% and negative predictive value from 62.1% to 99.7% depending on codes used. This means that few false positives are present in coded administrative data.

Rhee[35] reported results of an analysis of hospitalisation trends. This study demonstrated variation in predicted increases in hospitalisations depending on how sepsis was defined. Hospital-coded sepsis data show hospitalisations for sepsis are increasing over time (Figure 2).

Figure 2: Annual number of total hospitalisations according to sepsis definition, US hospitals, 2009–2014



The most recent hospital data published by the Australian Institute of Health and Welfare describe numbers of hospital separations (admissions) for sepsis and the number of days people were in hospital in total.[36] These data are an underestimate of the true number of hospital separations as they are limited to people whose principal diagnosis was sepsis and do not include patients who were in hospital for another reason but also had sepsis during their admission.

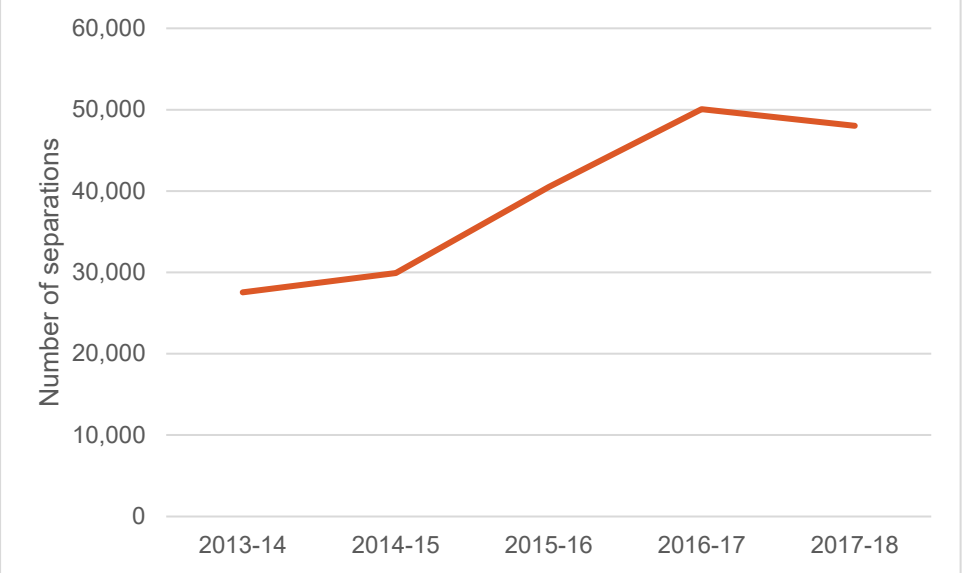
Using ICD-10 codes consistent across definitions described by Jolley[12], there were 48,005 hospitalisations in 2017–18 in Australia, accounting for a total of 381,203 bed days, where the main reason the person was hospitalised was sepsis (Table 3). This represents 0.4% of all hospitalisations and 25% of infectious diseases hospitalisations.

Table 3: Hospital separations according to principal diagnosis, Australia, 2013–14 to 2017–18

ICD Code	2017–18	2016–17	2015–16	2014–15	2013–14
A40–40.9 Streptococcal sepsis	3,472	3,382	2,681	2,257	2,177
A41–41.9 Other sepsis	40,185	42,358	33,941	24,359	22,182
O85 Puerperal sepsis	1,440	1,440	1,394	1,265	1,358
P36 Bacterial sepsis of newborn	2,908	2,883	2,493	2,045	1,834

The total number of sepsis-related separations has increased over time in Australia (Figure 3).

Figure 3: Separations, sepsis ICD-10 codes, Australia, 2013–14 to 2016–17



Some people are admitted to hospital multiple times for sepsis. Published data do not include the number of patients that account for these 48,005 hospitalisations.

The Australian Sepsis Network reports the annual incidence of sepsis in the adult Australian population treated in an ICU is 0.77 per 1,000 population, corresponding to more than 15,700 new cases per year.[37,38] These data are from an analysis in 2004. We did not identify any more recent sources of data in the public domain that describe ICU utilisation for sepsis, or that include paediatric sepsis. We note the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE) and the Paediatric Study Group have a number of clinical trials that have been published or are underway regarding intensive care management of adults and paediatric patients with sepsis. These are described on the ANZICS website[39].

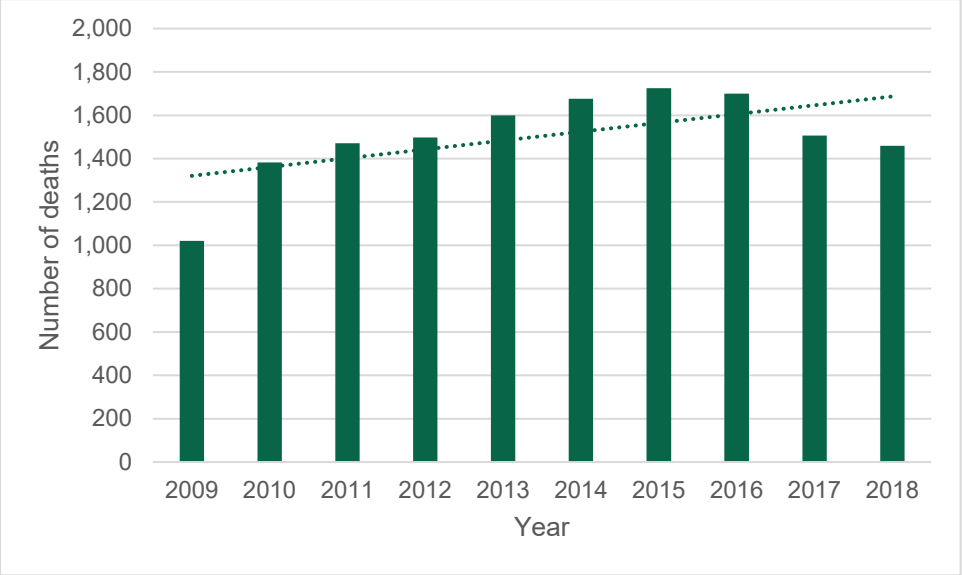
Sepsis as an underlying cause of death

According to the most recent data available from the Australian Bureau of Statistics[40] (2018 calendar year), there were 1,434 people (excluding newborns) whose underlying cause of death was recorded as sepsis. This represents 0.9% of all deaths in Australia that year.

There were more females who died from sepsis (757 people) than males (677 people). There were no deaths from puerperal sepsis in 2018 or from other puerperal infections. Bacterial sepsis of the newborn was associated with 25 deaths in 2018 – 13 males and 12 females.

In the 10 years to 2018 there has been an upward trend in sepsis as an underlying cause of death to 2015, after which deaths began to decrease.[40]

Figure 4: Sepsis as underlying cause of death, Australia, 2009 to 2018*



* Based on ICD Groupings: A40–40.9 Streptococcal sepsis, A41–41.9 Other sepsis, O85 Puerperal sepsis, P36 Bacterial sepsis of newborn.

In this 10-year period, bacterial sepsis of the newborn and puerperal sepsis was the underlying cause of death in 289 and 12 people, respectively.

These data are an underestimate of the true number of deaths associated with sepsis. The Global Burden of Disease (Sepsis) Study used data from 109 million death records and 8.6 million hospital records in 195 countries to estimate the burden of sepsis worldwide. These data suggest approximately 8,700 deaths per year in Australia are associated with sepsis – an age-standardised mortality rate of 19.9 per 100,000 population.[29]

Observed increases in the number of hospital separations for sepsis may reflect true increases in sepsis disease burden. Alternatively, changes in hospital coding practices may contribute to the observed rise.

The same increase is observed in sepsis deaths. Coding systems for deaths data are separate to hospital separations in each jurisdiction.

Question 2: Does Australia have better or worse outcomes for people who survive sepsis?

There are very few available data that compare outcomes from sepsis in Australia compared with other countries. We could only find one systematic review that reported comparative mortality as an outcome of sepsis diagnosis across countries internationally.

Bauer[9] conducted a systematic review (170 RCTs and cohort studies, 371,937 adults with sepsis or septic shock, low-quality review) that demonstrated the 30-day septic shock mortality in Australia is lower than mortality in North America and Europe. Mortality rates varied between regions, with 30-day septic shock mortality being 33.7% (95% CI 31.5–35.9) in North America, 32.5% (95% CI 31.7–33.3) in Europe and 26.4% (95% CI 18.1–34.6) in Australia. A statistically significant decrease of 30-day septic shock mortality rate was found between 2009 and 2011, but not after 2011.

The Global Burden of Disease Study (Sepsis)[29] compares incidence of sepsis across 195 countries. According to the results of this study the age-standardised incidence of sepsis in Australia is estimated by the authors as 158.8 cases per 100,000 population per year. This is much lower than countries with the highest incidence of sepsis (3,400 to 4,300 cases per 100,000 people per year). Age-standardised mortality is also lower; the estimated age-standardised mortality rate in Australia is 19.9 per 100,000 population. This is lower than high-income North America (33.8 per 100,000 population), the United Kingdom (34.8 per 100,000 population) and Western Europe (25.7 per 100,000 population).

Question 3: What complications do survivors of sepsis face?

Approximately half of patients who survive a hospitalisation for sepsis achieve a complete or near complete recovery at two years after discharge; one third of these patients die during this period; and one sixth of these patients remain with one or more complications.[18]

Increased premature mortality

The majority of published studies that examine sepsis outcomes use mortality as a primary endpoint. Overall, these studies demonstrate sepsis diagnosis is associated with increased premature mortality in adults. However, wide variation in estimates of sepsis mortality is described across published studies. Impacts of sepsis on premature mortality in paediatric survivors of sepsis are not well described in included studies in this review.

Bauer[9] (170 studies, 371,937 patients, low quality review) reported that for adults with sepsis the average septic shock mortality at 90 days is 38.5% (95% CI 35.4–41.5%) and average sepsis mortality at 90 days is 32.2% (95% CI 27.0–37.5%). Septic shock is a stage of sepsis often leading to death.

Alam[7] (16 studies, 5,333 participants, low quality review) examined mortality in adults admitted to ICU with sepsis. Accumulated mortality after discharge was measured at one or more time points after discharge. In three studies, mortality was measured up to six months after discharge. In these studies, mortality rate was between 30% and 45%. Seven studies looked at long-term mortality up to five years after discharge and their mortality rates ranged between 9.5% and 67%.

Shankar-Hari[20] (59 studies, 1.45 million adult patient episodes, critically low-quality review) assessed the relationship between sepsis and long-term mortality. In patients who survived an index sepsis admission, one-year mortality was 16.1% (95% CI 14.1 to 18.1%). There was substantial heterogeneity between studies.

Higgins[22] published results of a randomised controlled trial (1,591 patients, low risk of bias) including Australian participants (85% of patient cohort) presenting to the emergency department with early septic shock (defined as suspected or confirmed infection, two or more criteria for systemic inflammatory response and evidence of refractory hypotension or hypoperfusion). The 90-day, six-month, and one-year mortality were 21.8–22.6% at six months, and 26.4–27.9% at 12 months.

Shankar-Hari[24] described the following risk factors for increased post-acute mortality – older age, male sex and presence of comorbidities, including pneumonia, immunosuppression, cardiovascular disease, malignancy and renal insufficiency requiring dialysis. In addition, tobacco use was identified as a risk factor for increased post-acute mortality.

Other included studies in this review have examined risk factors for premature mortality after sepsis, including older age, obesity, diabetes and cardiac dysfunction and premature mortality in patients with sepsis. Results from these studies show:

- Mortality at one-year follow-up is higher in patients aged >80 years admitted to ICU with sepsis according to findings from a review by Haas[11] (18 studies, 4,256 patients, low quality review); their median one-year mortality was 68% (95% CI 53%–83%); one-year mortality was not reported for any Australian patient cohort in this review
- Mortality at one-year follow-up is not increased in adults with obesity according to the findings of a systematic review by Robinson[19] (nine observational studies, 1.8 million patient episodes, critically low-quality review)

- There is currently insufficient evidence that diabetes is associated with premature mortality in adult patients with sepsis (Wang[21], 10 studies, 261,342 patients, low quality review)
- The impact of cardiac dysfunction (global longitudinal strain measured with speckle-tracking echocardiography) on mortality is uncertain according to the results of a systematic review by Vallabhajosyula[15] (5 studies, 561 participants, low quality review).

There is insufficient evidence to describe premature mortality in paediatric survivors of sepsis. Menon[13] conducted a meta-analysis of primary outcome measures in paediatric septic shock trials (19 studies, low quality review). Mortality was the most common primary outcome measure of studies. Fourteen of the 19 included studies reported mortality. However, only five reported mortality at 28 days – the longest follow-up of patients in any of the included studies.

We identified two recent observational studies not assessed for inclusion in included systematic reviews.

- Schuler[25] (cohort study, 30,163 patients, good quality study) assessed long-term survival in patients with sepsis and acute organ dysfunction; there were 30,163 patients admitted through the emergency department with sepsis who were followed post-discharge; a diagnosis of acute neurological dysfunction during hospital admission was associated with increased long-term mortality at one year (6% increase in marginal predicted probability of mortality, 95% CI 5% to 7%)
- Shankar-Hari[24] (cohort study, 94,748 patients, good quality study) assessed the relationship between risk factors at index hospitalisation and mortality in adults with sepsis treated in critical care units; at one year after hospital discharge, 15% of sepsis survivors had died, with 6% to 8% dying per year over the subsequent five years; age, sex, race/ethnicity, severe comorbidities, dependency, being a non-surgical rather than surgical patient and site of infection were independently associated with long-term mortality.

Cognitive functional impairments

People who survive sepsis may experience cognitive dysfunction. In some patients, cognitive changes are long-term. Severity of cognitive impact seems to be positively correlated with the severity of the sepsis episode.

Calsavara[10] (16 studies, >74 million patient episodes, low quality review) found post-sepsis cognitive impairment is observed in 12.5–21% of adult survivors. Attention, cognitive flexibility, processing speed, associative learning, visual perception, work memory, verbal memory, and semantic memory were the specific domains affected. Depressive symptoms, central nervous system infection, length of hospitalisation due to infection and temporal proximity to the last period of infection were positively associated with the presence of cognitive impairment.

Barichello[8] (20 clinical studies, low quality review) examined long-term cognitive outcomes after sepsis. Included clinical studies showed that sepsis survivors experienced increased neuropsychiatric problems compared to before sepsis. In adults, severe sepsis was associated with more severe cognitive dysfunction. Although the percentage of people affected decreased over time, persistent cognitive impairment affected a subgroup of patients.

- A randomised controlled trial that followed patients with sepsis-associated respiratory distress found that 36–38% of patients at six months had cognitive deficiency; by 12 months this had decreased to 28–30% of patients
- An observational cohort study of over 637,867 adult survivors of severe sepsis found three quarters of survivors had functional disability at three years follow-up and 15% had severe cognitive dysfunction
- Severe sepsis was independently associated with a subsequent dementia diagnosis in older patients treated in intensive care in one included observational study, however, dementia was common in all older patients who were treated in intensive care; a study of 25,367 older adults who were treated in intensive care and survived found 17.8% were newly diagnosed with dementia in the three years post-discharge.

Barichello[8] described included studies that demonstrated sepsis is associated with subsequent cognitive impairment in children:

- Children who survived sepsis-associated encephalopathy presented delayed neurodevelopment, low verbal IQ, weakening in school performance, and lower intelligence scores at short-term follow-up
- An observational study of children (median age 4.2 years, median age at follow-up 10.7 years) found 44% had cognitive scores < 25% of the general population; rates of anxiety and depression and health-related quality of life were equivalent to the general population.

Haller[4] conducted a meta-review of neurological sequelae of sepsis in very low birthweight infants. Two systematic reviews (6,092 patients, moderate quality review) were included and showed that, compared with very low-birthweight babies who had not been diagnosed with sepsis, very low- birthweight babies who had survived sepsis had significantly higher risk of subsequent neurodevelopmental impairment (Risk Difference 13% (95% CI 5% to 20%) and vision impairment (RD 9% (95% CI 7% to 11%) but not hearing impairment (RD 4% (95% CI -2% to 10%). Very low-birthweight babies who survived sepsis had higher risk of subsequent diagnosis of cerebral palsy (RD 8% (95% CI 6% to 10%).

Barichello[8] described included studies that demonstrated survivors of sepsis may also experience increased mental health disease burden:

- A prospective cohort study of 135 patients after sepsis demonstrated 5% subsequently developed severe depression. however, another cohort study of 439 patients with severe sepsis found 28% had depression at 1.2 years before sepsis diagnosis and that incidence of depression did not change significantly at 11 months follow-up
- A study of 447 patients with severe sepsis showed 38% had depression with normal cognition before their sepsis diagnosis – 18% developed incident cognitive impairment after their sepsis diagnosis; these data suggest pre-sepsis depressive symptoms are predictive of post-sepsis incident cognitive impairment
- The mental health impacts of severe sepsis have also been observed on spouses – a retrospective cohort study of 55 patients treated in intensive care with severe sepsis and followed for 55 months after discharge showed 26% of patients and 42% of spouses showed clinically measurable anxiety or depression.

Ehlenbach[31]conducted a data linkage study that assessed cognitive impairment in patients who survived severe sepsis – a total of 5% of Medicare patients discharged to a skilled nursing facility. MDS-COGS was used to assessed cognitive function and MDS ADL to assess functional dependence. Discharge to a skilled nursing facility was associated with shorter survival, and cognitive impairment and activities of daily living (ADL) dependence were each strongly associated with shortened survival. Of 66,540 beneficiaries admitted to a skilled nursing facility, 34% had severe or very severe cognitive impairment, and 72.5% had maximal, dependence, or total dependence in ADL. The adjusted hazard ratio for death was 3.1 for those with very severe cognitive impairment relative to those who were cognitively intact (95% CI 2.9 to 3.2), and 4.3 for those with "total dependence" in ADLs relative to those who were independent (95% CI 3.8 to 5.0, p<0.001).

Physical functional impairments

People who survive sepsis may also experience changes to physical function. Severity of impacts on physical function appear to be positively correlated with the severity of the sepsis episode.

Bertazone[16] (seven studies, critically low-quality review) described an association between sepsis and physical function/physical fitness. Survivors of sepsis were shown to be at increased risk of impairments related to physical fitness and/or physical conditioning and physical function after hospital discharge, resulting in loss of independence and autonomy in carrying out the activities of daily living. Impacts were greatest in patients who had survived septic shock.

Barichello[8] described results of a voluntary online survey of 1,475 sepsis survivors. Survivors reported a broad range of symptoms – body numbness, fatigue, pain, chest pain, palpitations, visual disturbances, stomach and eating problems, memory loss, mood changes, hair loss, problems with dentition and nails and reduced satisfaction with sex drive. Sepsis survivors also reported decreased ability to perform chores, walk up and down stairs, walk for at least 15 minutes, run errands, adequately spell when writing and read for at least 15 minutes.

We identified recent observational studies by Gardner[27] and Mankowski[26] that described physical function after hospital discharge for sepsis.

- Gardner followed 173 patients after treatment in a surgical ICU; patients who developed chronic critical illness during their ICU admission had significantly lower physical function (physical performance, hand group) at six months compared with patients who showed rapid recovery after ICU admission for sepsis[27]
- Mankowski 2020 followed 328 patients treated in a surgical ICU for sepsis; the authors found that, compared with younger patients, older patients (aged 65 years and over) had significantly more comorbidities, intra-abdominal infections, septic shock and organ dysfunction – older people were more likely to progress into chronic critical illness and have poorer physical function (measured with Zubrod Performance Status) to 12 months.[26]

Paediatric populations

Few included studies reported outcomes associated with sepsis in paediatric patients. Available evidence demonstrates sepsis is associated with increased risk of retinopathy of prematurity (ROP) in preterm infants (Wang[6], 16 studies, 12,466 participants, moderate quality review). Adjusted analysis showed that sepsis was closely related to any stage of ROP (OR 1.57, 95% CI 1.31 to 1.89) and severe stage of ROP (OR 2.33, 95% CI 1.21 to 4.51) in premature infants. However, considering that all included studies are observational, and causality can rarely be established, additional evidence is needed to substantiate this finding and provide advice for practice. Huang[17] published results of a critically low-quality systematic review on the same topic – results are not considered further here. The review is described at Appendix D.

Quality of life impacts

Bertazone[16] included seven observational studies and found the health-related quality of life (HRQOL) of patients who had experienced a severe sepsis episode generally improves over time. However, some patients are left with residual physical function deficits that interfere with HRQOL.

Alam[7] (16 observational studies, 5,333 patients, low quality review) examined long-term health related quality of life in patients with sepsis after intensive care stay.

- Most included studies (81.3%) concluded patients treated in ICU for suffer from impaired quality of life; quality of life is impacted in all patients treated in ICU, not just patients with a sepsis diagnosis; four studies comparing HRQOL with other critically ill ICU survivors without sepsis, found that sepsis survivors have a similar HRQOL
- Compared with age- and/or gender-matched population controls, significant reductions in HRQOL were observed in physical as in social domains of life; the longest length of follow-up was six years – HRQOL impacts persisted in some patients up to this time point.

Quality of life data from Australian patients were published by Higgins[22] (1,591 patients, low risk of bias) in a randomised controlled trial of adult participants presenting to the emergency department with early septic shock randomised to early goal directed therapy or usual care. HRQOL data were available for 85.1% of survivors at 12 months. The authors found the only independent predictor of HRQOL at 12 months was age. Quality of life measures (all domains of the EQ-5D-3L, EQ VAS and utility scores, all SF-36 domains and AQoL utility scores) showed quality of life was significantly lower in sepsis survivors compared with age-matched population norms at all time points to 12 months post-hospitalisation. Improvements were observed between baseline and 12 months follow-up in some but not all quality of life measurement tools.

We identified one observational study not assessed for inclusion in included systematic reviews. Su[28] (case control study, 612 participants, poor quality study) assessed quality of life in adult ICU patients with and without sepsis. At three months after discharge there were no significant differences in the eight dimensions of the SF36 scale, the EQ-5D health utility scores, and the activities of daily life scores between septic survivors and non-septic survivors. However, compared with the quality of life of the general population (aged 55–64 years), the quality of life of patients with sepsis was significantly lower at three months after discharge ($p < 0.05$). Quality of life improved significantly between three months and two years follow-up. Older age, female gender and longer mechanical ventilation time were the risk factors associated with poorer quality of life.

Other chronic disease morbidity

Prescott[18] (critically low-quality review) reported results from studies that described clinical sequelae of sepsis. According to results of this review:

- Patients are susceptible to recurrent infection after sepsis
- Patients discharged after treatment for sepsis have high rates of hospital readmission for pre-existing chronic conditions including heart failure, renal failure and chronic obstructive pulmonary disease
- Risk of cardiovascular events is increased after sepsis diagnosis (myocardial infarction, stroke, sudden cardiac death, ventricular arrhythmias).

The UK Sepsis Trust Sepsis Manual describes Post-Sepsis Syndrome (PSS) affecting survivors of sepsis, particularly those treated in ICU.[41] This is a term used to describe a group of problems that commonly occur following sepsis, which fall into one of three categories: physical, cognitive and psychological. PSS can affect people of any age, it commonly takes six to 18 months to recover, with some survivors taking considerably longer and some never resuming their pre-sepsis state of health again. Physical features include lethargy/excessive tiredness, poor mobility/muscle weakness, breathlessness, chest pains, vertigo, swollen limbs, joint pains, hair loss, dry/flaking skin and nails, taste changes, poor appetite, changes in vision, changes in limb sensation, repeated infections and reduced kidney function. Psychological and cognitive features include anxiety, depression, flashbacks, nightmares, insomnia, post-traumatic stress disorder, poor concentration, short term memory loss, mood changes and loss of confidence and self-esteem.

Question 4: How frequently are survivors readmitted to hospital?

We identified one systematic review and one data linkage study that addressed this question.

Shankar[14] (56 studies, 6.7 million patient episodes, low quality review) examined rate and risk factors for re-hospitalisation in survivors of sepsis.

Included studies most often reported the 30-day re-hospitalisation rate. The mean rate of re-hospitalisation at 30 days was 21.4% (95% CI 17.6–25.4%). Rate of re-hospitalisation increased over time, from 9.3% (95% CI 8.3–10.3%) by 7 days to 39.0% (95% CI 22.0–59.4%) by one year. Infection was the most common reason for re-hospitalisation.

Risk factors that increased the re-hospitalisation risk in sepsis survivors were older age, male gender, comorbidities, non-elective admissions, hospitalisation prior to index sepsis admission and sepsis characteristics such as infection and illness severity, with hospital characteristics showing inconsistent associations.

Buchman[30] conducted a data linkage study that assessed illness trajectories of Medicare beneficiaries after hospital admission for sepsis. Discharge destinations of patients were to a skilled nursing facility (23.8%), hospice (7.2%) or home (57.1%). Approximately 28% were readmitted to hospital in the following six months, 11.6% for sepsis.

Question 5: What interventions improve recovery after discharge and reduce ongoing morbidity?

Patient goals and wishes are for improved quality of life and return to normal function after sepsis diagnosis.[32] Few studies have been conducted to identify interventions that successfully improve quality of life or function. Available evidence indicates sepsis survivors, their families and caregivers require information about their diagnosis, prognosis and follow-up care needs. Some patients require additional assistance navigating the health system to access appropriate and specialised follow-up care in the community, due to the risk of sequelae.

NICE guidelines report the results of a review of the literature to identify what information, education and support are useful for people who survive an episode of sepsis.[1] The authors identified a qualitative study of the needs and aftercare of children surviving meningitis and/or septicaemia and a qualitative study of adults who had survived an episode of severe sepsis in the previous 12 months, which included caregivers, family members and friends.

The paediatric study reported a need to support families to navigate the health system after sepsis survival. Participants reported a need for a debrief from health providers before discharge and that parents should be involved in communications about aftercare. Most parents reported that their child required after care and support, the greatest need being for educational support (30% of participants). People accessed a variety of follow-up services for hearing, speech and language, occupational therapy, behavioural, psychological or emotional support. Note, this study combined results from meningitis survival with sepsis survival. Results were not reported separately for each patient group.

The adult study reported wide variation in participants' awareness of severe sepsis as a diagnosis and understanding of severe sepsis. Some were not aware of their diagnosis until being invited to take part in the study. Time in intensive care was reported by caregivers as being frightening and worrying. Lasting impacts of sepsis varied and included sensory, cognitive, physical appearance, symptoms from complications, medication side effects and loss of mobility. Difficulties with self-care during recovery were reported. Caregivers reported increased caring burden, reduced freedom and lasting emotional impacts, including frustration, guilt, anxiety and stress. Patients received a general lack of information about their diagnosis, what to expect during recovery and how to access follow-up community treatment.

Konig conducted a qualitative analysis to identify how sepsis survivors conceptualise health-related quality of life. Eleven domains emerged as critically important: psychological impairment, fatigue, physical impairment, coping with daily life, return to normal living, ability to walk, cognitive impairment, self-perception, control over one's life, family support and delivery of health care. Sepsis survivors want a "normal life," to walk again, and to regain control without cognitive impairment. Studies of interventions that target the quality of life goals and wishes identified by Konig were not identified in our review.

Prescott described results of an International Sepsis Forum colloquium convened in February 2018 to identify priorities for understanding and enhancing sepsis survivorship.[33] There were 26 experts from eight countries who participated. Participants identified important research gaps and concluded there are few studies of in-hospital or post-hospital interventions to enhance longer-term survival and quality of life. There is a need for research to identify patients most likely to benefit from interventions.

We certainly found very little evidence for interventions to improve mortality, morbidity or quality of life in patients after sepsis diagnosis. We found one study that searched for but did not identify evidence for rehabilitation interventions after hospital discharge. Another study assessed a primary care intervention, which had little impact on patient goals and wishes identified by Konig. The detail of these two studies is as follows:

- Taito[3] (2 studies, 75 patients, high quality review) examined rehabilitation interventions to improve recovery in patients with sepsis. The authors only identified two RCTs, both conducted in an ICU setting. No trials of community rehabilitation were identified in the searches. Results from included studies showed rehabilitation did not significantly decrease ICU mortality, ICU length of stay or hospital length of stay and muscle strength was not statistically significantly different. The certainty of the evidence for these outcomes was “very low.” Data on activities of daily living, return to work or delirium were not available in either trial.

- Schmidt[23] (RCT, 291 patients, high risk of bias) reported results of a primary care intervention to improve mental and physical sequelae of sepsis. The intervention included training of patients and their general practitioners in evidence-based post-sepsis care, case management provided by a trained nurse and clinical decision support for GPs by consulting physicians. Both the intervention and control group (usual care) experienced improvement in function to two years follow-up. Patients in the usual care group experienced significantly higher disease burden from post-traumatic stress disorder than the intervention group.

We also included one critically low-quality review by Prescott[18] that reported evidence for inpatient and outpatient interventions to enhance recovery. For inpatients, the authors found that hospital and ICU-based strategies to prevent adverse complications after sepsis in the literature focus on short-term mortality, with little focus on minimising physical disability, cognitive impairment or health deterioration after sepsis. Nevertheless, they proposed the following inpatient strategies for preventing long-term complications after sepsis:

- High-quality early sepsis care
- Management of pain, agitation, and delirium
- Early mobilisation to prevent or minimise muscle atrophy.

For outpatients, the authors report there is limited clinical trial evidence to guide management of patients after hospital discharge. They described randomised controlled trials that have examined:

- Specialised nurse-led ICU follow-up clinics (two studies, 672 patients, follow-up one year)
- In-person exercise rehabilitation programs (three studies, 275 adult ICU survivors, follow-up three to six months)
- Provision of self-guided exercise rehabilitation manuals (one study, 126 patients, follow-up six months)
- Case management interventions (two studies, 625 adult ICU survivors, follow-up two months to one year).

Prescott found these interventions have yielded small and inconsistent benefits in short- and moderate-term physical function by patient report or physical assessment.

The authors also included one observational study of 30,000 sepsis survivors which showed that referral to rehabilitation within 90 days of hospital discharge was associated with lower risk of 10-year mortality compared with propensity-matched controls (adjusted HR, 0.94; 95% CI, 0.92–0.97; P < .001). Another included study was a small pilot RCT of a multicomponent post-ICU rehabilitation program incorporating cognitive, functional, and physical rehabilitation. Results showed improved cognitive and functional outcomes at three months using the Tower test for planning and strategic thinking, suggesting that neurocognitive deficits may be also be amenable to treatment.

In the absence of evidence of effectiveness, the authors propose a framework for evaluating and treating patients in the 90 days after hospitalisation for sepsis that includes the following elements:

1. Screen for common, treatable impairments after sepsis (functional disability, swallowing impairment, mental health impairments); and
2. Review and adjust long-term medications (evaluate and manage to reduce medication errors, manage medications to reduce heart failure exacerbations, acute renal failure sequelae and chronic obstructive pulmonary disease exacerbations).

Conclusion

We identified 32 publications of broad relevance to the review: one guideline, 19 systematic reviews, two randomised controlled trials, five observational studies, two qualitative studies, two data linkage analyses and one burden of disease study.

The key findings of this review were:

- The number of Australians who survive sepsis each year is largely unknown
- Available evidence suggests Australia has a lower incidence of sepsis and lower 30-day septic shock mortality compared with North America and Europe
- Sepsis diagnosis is associated with increased premature mortality in adults
- People who survive sepsis are at increased risk of subsequent premature mortality, recurrent infection, impaired cognitive or physical function and reduced quality of life; one in five people will be re-admitted to hospital within 30 days of hospital discharge after sepsis
- People who survive sepsis may experience cognitive impairment; this has been observed in adults and children after sepsis; children and neonates may also experience neurodevelopmental impacts, vision and hearing impairment
- There are few studies that have explored interventions to improve recovery after hospital discharge and to reduce ongoing morbidity after sepsis
- Available evidence indicates sepsis patients, their families and caregivers require information about their diagnosis, prognosis and where they can receive support for their ongoing care needs
- Some people need assistance navigating the health system to access the follow-up care they require after treatment for sepsis
- Caregivers report an increased caring burden for patients following sepsis and may need access to additional services and resources to provide support.

This review demonstrated that there is very little evidence for specific interventions – developed, trialled or implemented – to improve mortality, morbidity or quality of life in patients after hospital discharge for sepsis. Future opportunities exist to address knowledge gaps and improve post-hospital discharge sepsis support services. This includes conducting research to identify effective strategies that improve survival, quality of life and cognitive and physical function in people who have survived sepsis.

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Appendices

Appendix A: Literature review search terms

No.	Search term
#1	exp Sepsis [MeSH] OR sepsis[tiab]
#2	Clinical pathway[mh] OR Clinical protocol[mh] OR Consensus[mh] OR Consensus development conferences as topic[mh] OR Critical pathways[mh] OR Guidelines as topic [Mesh:NoExp] OR Practice guidelines as topic[mh] OR Health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt] OR consensus development conference[pt] OR consensus development conference, NIH[pt] OR position statement*[tiab] OR policy statement*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR standards[ti] OR guideline[ti] OR guidelines[ti] OR ((practice[tiab] OR treatment*[tiab]) AND guideline*[tiab]) OR CPG[tiab] OR CPGs[tiab] OR consensus*[tiab] OR ((critical[tiab] OR clinical[tiab] OR practice[tiab]) AND (path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR protocol*[tiab])) OR recommendat*[ti] OR (care[tiab] AND (standard[tiab] OR path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR map[tiab] OR maps[tiab] OR plan[tiab] OR plans[tiab])) OR (algorithm*[tiab] AND (screening[tiab] OR examination[tiab] OR test[tiab] OR tested[tiab] OR testing[tiab] OR assessment*[tiab] OR diagnosis[tiab] OR diagnoses[tiab] OR diagnosed[tiab] OR diagnosing[tiab])) OR (algorithm*[tiab] AND (pharmacotherap*[tiab] OR chemotherap*[tiab] OR chemotreatment*[tiab] OR therap*[tiab] OR treatment*[tiab] OR intervention*[tiab]))
#3	meta-analysis.pt. or meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. or ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. or (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. or (handsearch* or hand search*).ti,ab,kf,kw. or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. or (meta regression* or metaregression*).ti,ab,kf,kw. or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. or (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. or (cochrane or (health adj2 technology assessment) or evidence report).jw. or (meta-analysis or systematic review).mp. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. or (outcomes research or relative effectiveness).ti,ab,kf,kw. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.
#4	#1 AND #2 AND #3
#5	#4 NOT (Comment OR Congress OR Editorial OR Letter OR News).pt.
#6	limit to yr="2015 -Current"

Appendix B: Excluded full-text publications

	Publication	Reason for exclusion
1	Xie RR, Xie JF, Yang Y. [Long-term prognosis and management in patients with sepsis]. Zhonghua Nei Ke Za Zhi. 2019;58(4):329–32.	Article in Chinese
2	Yu L, Sun R. [Evaluation and treatment of sepsis-induced myocardial dysfunction: a systematic study]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019;31(3):378–80.	
3	Hartog CS, Bodechtel U, Fleischmann-Struzek C, Denke C, Weiss B, Reinhart K. [Sepsis: Sequelae for Affected Patients and The Health Care System]. Dtsch Med Wochenschr. 2020;145(4):252–9.	Article in German
4	Jette AM. Enhancing Recovery After Sepsis. Phys Ther. 2018;98(6):459–60.	Editorial
5	Shi Q, Mu X, Hong L, Zheng S. SERPINE1 rs1799768 polymorphism contributes to sepsis risk and mortality. J Renin Angiotensin Aldosterone Syst. 2015;16(4):1218–24.	Gene polymorphism study
6	Tan B, Wong JJ, Sultana R, Koh J, Jit M, Mok YH, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. Jama, Pediatr. 2019;173(4):352–62.	In-hospital and post-discharge mortality not analysed separately
7	Ahn JY, Song JE, Ann HW, Jeon Y, Ahn MY, Jung IY, et al. Effects of early exercise rehabilitation on functional recovery in patients with severe sepsis. Yonsei Med J. 2018;59(7):843–-51.	In-hospital intervention
8	ISicong W, Xu L, Qixing C, Can L, Changshun H, Xiangming F. The role of increased body mass index in outcomes of sepsis: a systematic review and meta-analysis. BMC Anesthesiology. 2017;17:1–11.	Inpatient analysis
9	Ward HH, Kiernan EA, Deschler CL, Murillo SM, Karoly EA, Macfarlan JE, et al. Clinical and demographic parameters of patients treated using a sepsis protocol. Clinical Therapeutics. 2019;41(6):1020–8.	Inpatient management using sepsis protocol
10	Thavamani A, Umapathi KK, Dhanpalreddy H, Khatana J, Chotikanatis K, Allareddy V, et al. Epidemiology, Clinical and microbiologic profile and risk factors for inpatient mortality in pediatric severe sepsis in the United States from 2003 to 2014: a large population analysis. The Pediatric Infectious Disease Journal. 2020;25.	Limited to inpatient mortality
11	Hsu WT, Galm BP, Schrank G, Hsu TC, Lee SH, Park JY, et al. Effect of renin-angiotensin-aldosterone system inhibitors on short-term mortality after sepsis: a population-based cohort study. Hypertension. 2020:483–91.	Limited to inpatients
12	Trivedi V, Bavishi C, Jean R. Impact of obesity on sepsis mortality: a systematic review. J Crit Care. 2015;30(3):518–24.	
13	Wang W, Chen W, Liu Y, Li L, Li S, Tan J, et al. Blood glucose levels and mortality in patients with sepsis: dose-response analysis of observational studies. Journal of Intensive Care Medicine. 2019.	

	Publication	Reason for exclusion
14	Workman JK, Bailly DK, Reeder RW, Dalton HJ, Berg RA, Shanley TP, et al. Risk factors for mortality in refractory pediatric septic shock supported with extracorporeal life support. ASAIO journal. Epub ahead of print. PMID 32205509. 2020.	
15	Wang J, Sun Y, Teng S, Li K. Prediction of sepsis mortality using metabolite biomarkers in the blood: a meta-analysis of death-related pathways and prospective validation. BMC Medicine. 2020;18(1).	Metabolic biomarker study
16	Arfaras-Melainis A, Polyzogopoulou E, Triposkiadis F, Xanthopoulos A, Ikonomidis I, Mebazaa A, et al. Heart failure and sepsis: practical recommendations for the optimal management. Heart Fail Rev. 2020;25(2):183–94.	Narrative review
17	Aspesberro F, Mangione-Smith R, Zimmerman JJ. Health-related quality of life following pediatric critical illness. Intensive Care Medicine. 2015;41(7):1235–46.	
18	Atterton B, Paulino MC, Povoa P, Martin-Loeches I. Sepsis associated delirium. Medicina (Kaunas). 2020;56(5).	
19	Duffy MK, Moloney-Harmon PA. Helping children survive sepsis. Nursing. 2015;45(2):34–40; quiz-1.	
20	Durning MV. Sepsis: A review for home healthcare clinicians. Home Healthc Now. 2020;38(4):188–92.	
21	Frydrych LM, Fattahi F, He K, Ward PA, Delano MJ. Diabetes and sepsis: risk, recurrence, and ruination. Front Endocrinol (Lausanne). 2017;8:271.	
22	Mostel Z, Perl A, Marck M, Mehdi SF, Lowell B, Bathija S, et al. Post-sepsis syndrome – an evolving entity that afflicts survivors of sepsis. Mol Med. 2019;26(1):6.	
23	Nwafor DC, Brichacek AL, Mohammad AS, Griffith J, Lucke-Wold BP, Benkovic SA, et al. Targeting the blood-brain barrier to prevent sepsis-associated cognitive impairment. J Cent Nerv Syst Dis. 2019;11:1179573519840652.	
24	Perner A, Rhodes A, Venkatesh B, Angus DC, Martin-Loeches I, Preiser JC, et al. Sepsis: frontiers in supportive care, organisation and research. Intensive Care Med. 2017;43(4):496–508.	
25	Prescott HC, Costa DK. Improving long-term outcomes after sepsis. Crit Care Clin. 2018;34(1):175–88.	
26	Prescott HC. Preventing chronic critical illness and rehospitalization: a focus on sepsis. Crit Care Clin. 2018;34(4):501–13.	
27	Hua M, Gong MN, Brady J, Wunsch H. Early and late unplanned rehospitalizations for survivors of critical illness. Critical Care Medicine. 2015;43(2):430–8.	No sepsis-specific data
28	Mankowski RT, Yende S, Angus DC. Long-term impact of sepsis on cardiovascular health. Intensive Care Med. 2019;45(1):78–81.	Non-systematic review

	Publication	Reason for exclusion
29	Marik PE, Varon J. Critical care for the respiratory specialist: Sepsis, delirium and long-term cognitive dysfunction: Prevention with the combination of Vitamin C, hydrocortisone and thiamine. Current Respiratory Medicine Reviews. 2018;14(1):23–8.	
30	Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, et al. Corticosteroids for treating sepsis in children and adults. Cochrane Database Syst Rev. 2019;12:CD002243.	Not post-recovery management of sepsis
31	Bermejo-Martin JF, Andaluz-Ojeda D, Almansa R, Gandia F, Gomez-Herreras JI, Gomez-Sanchez E, et al. Defining immunological dysfunction in sepsis: A requisite tool for precision medicine. J Infect. 2016;72(5):525–36.	
32	Scherag A, Hartog CS, Fleischmann C, Ouart D, Hoffmann F, König C, et al. A patient cohort on long-term sequelae of sepsis survivors: study protocol of the Mid-German Sepsis Cohort. BMJ Open. 2017;7(8):e016827.	
33	Wójcik B, Superata J, Nguyen HB, Szyguła Z. Exploration of different rehabilitation routes for sepsis survivors with monitoring of health status and quality of life: RehaSep Trial Protocol. Adv Ther. 2019;36(10):2968–78.	Study protocol
34	Shih CJ, Chao PW, Ou SM, Chen YT. Long-term risk of cardiovascular events in patients with chronic kidney disease who have survived sepsis: a nationwide cohort study. J Am Heart Assoc. 2017;6(2).	Subgroup of patients with chronic kidney disease

Appendix C: Publications included in review

Publication type	ID	Publication details
NICE guideline	1	National Institute for Health and Care Excellence (NICE). Sepsis: recognition, diagnosis and early management. 2016. Updated 2017.
Systematic review	1	Alam N, Nannan Panday RS, Heijnen JR, Van Galen LS, Kramer MH, Nanayakkara PW. Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review. Acute Medicine. 2017;16(4):164–9.
	2	Barichello T, Sayana P, Giridharan VV, Arumanayagam AS, Narendran B, Della Giustina A, et al. Long-term cognitive outcomes after sepsis: a translational systematic review. Molecular Neurobiology. 2019;56(1):186–251.
	3	Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019 – results from a systematic review and meta-analysis. Critical Care. 2020;24(1).
	4	Bertazone TM, de Aguiar SG, Bueno Júnior CR, Stabile AM. Physical fitness and physical function in survivors of sepsis after hospital discharge. Fisioterapia em Movimento. 2018;31(1):1–11.
	5	Calsavara AJ, Nobre V, Barichello T, Teixeira AL. Post-sepsis cognitive impairment and associated risk factors: a systematic review. Aust Crit Care. 2018;31(4):242–53.
	6	Haas LEM, van Dillen LS, de Lange DW, van Dijk D, Hamaker ME. Outcome of very old patients admitted to the ICU for sepsis: a systematic review. European Geriatric Medicine. 2017;8(5–6):446–53.
	7	Haller S, Deindl P, Cassini A, Suetens C, Zingg W, Abu Sin M, et al. Neurological sequelae of healthcare-associated sepsis in very-low-birthweight infants: umbrella review and evidence-based outcome tree. Euro Surveill. 2016;21(8):30143.
	8	Huang J, Tang Y, Zhu T, Li Y, Chun H, Qu Y, et al. Cumulative evidence for association of sepsis and retinopathy of prematurity. Medicine (Baltimore). 2019;98(42):e17512.
	9	Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jette N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. Crit Care. 2015;19:139.
	10	Menon K, McNally JD, Zimmerman JJ, Agus MS, O'Hearn K, Watson RS, et al. Primary outcome measures in pediatric septic shock trials: a systematic review. Pediatr Crit Care Med. 2017;18(3):e146–e54.
	11	Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. Jama. 2018;319(1):62–75.
	12	Robinson J, Swift-Scanlan T, Salyer J. Obesity and 1-year mortality in adults after sepsis: a systematic review. Biological Research for Nursing. 2020;22(1):103–13.
	13	Shankar-Hari M, Ambler M, Mahalingasivam V, Jones A, Rowan K, Rubenfeld GD. Evidence for a causal link between sepsis and long-term mortality: a systematic review of epidemiologic studies. Crit Care. 2016;20:101.

Publication type	ID	Publication details
	14	Shankar-Hari M, Saha R, Wilson J, Prescott HC, Harrison D, Rowan K, et al. Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. Intensive Care Medicine. 2020;46(4):619–36.
	15	Taito S, Taito M, Banno M, Tsujimoto H, Kataoka Y, Tsujimoto Y. Rehabilitation for patients with sepsis: A systematic review and meta-analysis. PLoS ONE. 2018;13(7):e0201292.
	16	Tsertsvadze A, Royle P, Seedat F, Cooper J, Crosby R, McCarthy N. Community-onset sepsis and its public health burden: a systematic review. Syst. 2016;5:81.
	17	Vallabhajosyula S, Rayes HA, Sakhuja A, Murad MH, Geske JB, Jentzer JC. Global longitudinal strain using speckle-tracking echocardiography as a mortality predictor in sepsis: a systematic review. J Intensive Care Med. 2019;34(2):87–93.
	18	Wang X, Tang K, Chen L, Cheng S, Xu H. Association between sepsis and retinopathy of prematurity: a systematic review and meta-analysis. BMJ Open. 2019;9(5):e025440.
	19	Wang Z, Ren J, Wang G, Liu Q, Guo K, Li J. Association between diabetes mellitus and outcomes of patients with sepsis: a meta-analysis. Med Sci Monit. 2017;23:3546–55.
Randomised controlled trials	1	Higgins AM, Peake SL, Bellomo R, Cooper DJ, Delaney A, Harris AH, et al. Quality of life and 1-year survival in patients with early septic shock: long-term follow-up of the Australasian resuscitation in sepsis evaluation trial. Crit Care Med. 2019;47(6):765-773.
	2	Schmidt KF, Schwarzkopf D, Baldwin LM, Brunkhorst FM, Freytag A, Heintze C, et al. Long-term courses of sepsis survivors: effects of a primary care management intervention. Am J Med. 2020;133(3):381–5.e5.
Non-randomised trials	1	Gardner AK, Ghita GL, Wang Z, Ozrazgat-Baslanti T, Raymond SL, Mankowski RT, et al. The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. Crit Care Med. 2019;47(4):566–73.
	2	Mankowski RT, Anton SD, Ghita GL, Brumback B, Cox MC, Mohr AM, et al. Older sepsis survivors suffer persistent disability burden and poor long-term survival. J Am Geriatr Soc. 2020.
	3	Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, Shah NH, et al. The impact of acute organ dysfunction on long-term survival in sepsis. Critical Care Medicine. 2018;46(6):843–9.
	4	Shankar-Hari M, Harrison DA, Ferrando-Vivas P, Rubenfeld GD, Rowan K. Risk factors at index hospitalization associated with longer-term mortality in adult sepsis survivors. JAMA Network Open. 2019;2(5).
	5	Su YX, Xu L, Gao XJ, Wang ZY, Lu X, Yin CF. Long-term quality of life after sepsis and predictors of quality of life in survivors with sepsis. Chin J Traumatol. 2018;21(4):216–23.

Publication type	ID	Publication details
Other study types	1	Buchman TG, Simpson SQ, Sciarretta KL, Finne KP, Sowers N, Collier M, et al. Sepsis among medicare beneficiaries: 2. The trajectories of sepsis, 2012–2018. Crit Care Med. 2020;48(3):289–301.
	2	Ehlenbach WJ, Gilmore-Bykovskyi A, Repplinger MD, Westergaard RP, Jacobs EA, Kind AJ, et al. Sepsis survivors admitted to skilled nursing facilities: cognitive impairment, activities of daily living dependence, and survival. Crit Care Med. 2018;46(1):37–44.
	3	Konig C, Matt B, Kortgen A, Turnbull AE, Hartog CS. What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. Quality of Life Research. 2019;28(3):637–47.
	4	Prescott HC, Iwashyna TJ, Blackwood B, Calandra T, Chlan LL, Choong K, et al. Understanding and enhancing sepsis survivorship. priorities for research and practice. Am J Respir Crit Care Med. 2019;200(8):972–81.
	5	Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395(10219):200–11.
Total	32	

Appendix D: Evidence review tables

Guideline

Guideline	
Bibliographic reference	National Institute for Health and Care Excellence (NICE). Sepsis: recognition, diagnosis and early management. 2016. Updated 2017.
Scope	This guideline covers the recognition, diagnosis and early management of sepsis for all populations.
Title	Sepsis: recognition, diagnosis and early management
Author(s)	Faust S, Beale R, Butler J, Carrol E, Nadel S, Newell J, O'Donnell J, Rowlands R, Simmonds M, Tavare A, Vaughan L, Wenman J, White C.
Institution(s)	National Institute for Health and Care Excellence
Year	2017
Last search for evidence	September 2017
Recommendations	Information and support for people with people who have sepsis, and their families and carers: Ensure a care team member is nominated to give information to families and carers, particularly in emergency situations such as in the emergency department. This should include an explanation that the person has sepsis, and what this means an explanation of any investigations and the management plan regular and timely updates on treatment, care and progress. ■ Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given. ■ Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed. ■ Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis. ■ Give people who have had sepsis and their families and carers information about national charities and support groups that provide information about sepsis and causes of sepsis. ■ Advise carers they have a legal right to have a carer's assessment of their needs and give them information on how they can get this.
Indicators/data collection mechanisms	None

Quality appraisal (AGREE II)	Score (1–7)
1. The overall objective(s) of the guideline is (are) specifically described.	7
2. The health question(s) covered by the guideline is (are) specifically described.	7
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7

4. The guideline development group includes individuals from all relevant professional groups.	7
5. The views and preferences of the target population (patients, public, etc.) have been sought.	7
6. The target users of the guideline are clearly defined.	7
7. Systematic methods were used to search for evidence.	7
8. The criteria for selecting the evidence are clearly described.	7
9. The strengths and limitations of the body of evidence are clearly described.	7
10. The methods for formulating the recommendations are clearly described.	7
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	7
12. There is an explicit link between the recommendations and the supporting evidence.	5
13. The guideline has been externally reviewed by experts prior to its publication.	7
14. A procedure for updating the guideline is provided.	7
15. The recommendations are specific and unambiguous.	7
16. The different options for management of the condition or health issue are clearly presented.	7
17. Key recommendations are easily identifiable.	7
18. The guideline describes facilitators and barriers to its application.	7
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	7
20. The potential resource implications of applying the recommendations have been considered.	7
21. The guideline presents monitoring and/or auditing criteria.	7
22. The views of the funding body have not influenced the content of the guideline.	7
23. Competing interests of guideline development group members have been recorded and addressed.	7
Overall quality	**Low**

Systematic reviews

Systematic review	1
Bibliographic reference	Alam N, Nannan Panday RS, Heijnen JR, Van Galen LS, Kramer MH, Nanayakkara PW. Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review. Acute Medicine. 2017;16(4):164-9.
Study type	Systematic review
Number of included trials	16
Search strategy	PubMed, Cochrane Library, EMBASE, PsychINFO and CINAHL searched to July 2016
Number of participants	5,333 patients with sepsis and hospitalised controls
Population	Adults admitted to ICU
Intervention	Patients with sepsis
Comparison	Patients with no sepsis or general or age and / or gender matched population controls
Relevant outcome measures	Health-related quality of life (HRQOL)
Study designs	Observational study
Outcomes	Sixteen studies were included, 13 (81.3%) reported that sepsis survivors suffer from impaired HRQOL in physical and mental domains which persist from months to years after a sepsis episode.
Source of funding	Not funded
Authors' conclusions	More focus on improving long-term outcomes for patients surviving sepsis and the ICU is needed
Comments	
Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
12. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
13. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
14. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
15. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**2**
Bibliographic reference	Barichello T, Sayana P, Giridharan VV, Arumanayagam AS, Narendran B, Della Giustina A, et al. Long-term cognitive outcomes after sepsis: a translational systematic review. Molecular Neurobiology. 2019;56(1):186-251.
Study type	Systematic review
Number of included trials	130 (20 clinical studies of relevance to this review)
Search strategy	PubMed/MEDLINE (National Library of Medicine), PsycINFO, EMBASE (Ovid), LILACS (Latin American and Caribbean Health Sciences Literature), IBECS (Bibliographical Index in Spanish in Health Sciences), and Web of
Number of participants	Not stated
Population	People who have survived sepsis
Intervention	N/A
Comparison	N/A
Relevant outcome measures	Neuropsychiatric manifestations, long term cognitive decline, major depression, delirium, quality of life, PTSD, paediatric neurodevelopment
Study designs	2 RCTs and 18 Observational (14 prospective cohort, 3 retrospective cohort, 1 case study)
Outcomes	A number of pre-clinical studies have shown an auto amplification of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin (IL)-1beta, and IL-6 in the first few hours after sepsis induction, also increased blood-brain barrier permeability, elevated levels of matrix metalloproteinases, increased levels of damage-associated molecular patterns were demonstrated. In addition, the rodents presented long-term cognitive impairment in different behavioral tasks that were prevented by blocking the mechanism of action of these inflammatory mediators. Clinical studies have showed that sepsis survivors presented increased bodily symptoms such as fatigue, pain, visual disturbances, gastrointestinal problems, and neuropsychiatric problems compared to before sepsis.

Source of funding	Institutional funding only
Authors' conclusions	Sepsis leaves the survivors with an aftermath of physiological, neuropsychiatric, and functional impairment.
Comments	Purpose of review was to evaluate mechanisms by which sepsis induces long-term neurological sequelae

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	N
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	P
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**3**
Bibliographic reference	Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019 – results from a systematic review and meta-analysis. Critical Care. 2020;24(1).
Study type	Systematic review and meta-analysis
Number of included trials	170

Search strategy	Articles published in PubMed or in the Cochrane Database, between 2009 and 2019 in English language and conducted in Europe, North America or Australia / New Zealand.
Number of participants	371,937
Population	Adults with sepsis or septic shock
Intervention	Any intervention
Comparison	Any comparator
Relevant outcome measures	30-day and 90-day mortality
Study designs	RCTs, cohort studies
Outcomes	Average 30-day septic shock mortality was 34.7% (95% CI 32.6–36.9%), and 90-day septic shock mortality was 38.5% (95% CI 35.4–41.5%). Average 30-day sepsis mortality was 24.4% (95% CI 21.5–27.2%), and 90-day sepsis mortality was 32.2% (95% CI 27.0–37.5%). Estimated mortality rates from RCTs were below prospective and retrospective cohort studies. Rates varied between regions, with 30-day septic shock mortality being 33.7% (95% CI 31.5–35.9) in North America, 32.5% (95% CI 31.7–33.3) in Europe and 26.4% (95% CI 18.1–34.6) in Australia. A statistically significant decrease of 30-day septic shock mortality rate was found between 2009 and 2011, but not after 2011. Per 1-point increase of the average SOFA score, average mortality increased by 1.8–3.3%.
Source of funding	CytoSorbents Europe
Authors' conclusions	Trends of lower sepsis and continuous septic shock mortality rates over time and regional disparities indicate a remaining unmet need for improving sepsis management. Further research is needed to investigate how trends in the burden of disease influence mortality rates in sepsis and septic shock at 30- and 90-day mortality over time.
Comments	Studies with < 20 participants were excluded.

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	N
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**4**
Bibliographic reference	Bertazone ATM, Silva de Aguiar GC, Roberto Bueno Júnior C, Stabile AM. Physical fitness and physical function in survivors of sepsis after hospital discharge. Fisioterapia em Movimento. 2018;31(1):1–11.
Study type	Systematic review
Number of included trials	7
Search strategy	LILACS, PubMed, CINAHL, Cochrane Library, Web of Science and Scopus to November 2014
Number of participants	Not provided
Population	Adult patients who survived sepsis, severe sepsis or septic shock
Intervention	N/A
Comparison	N/A
Relevant outcome measures	Physical function or physical fitness
Study designs	Observational (2 prospective cohort, two cross-sectional, four longitudinal not specified and one mixed prospective cohort and cross-sectional)
Outcomes	No study applied a specific physical test to assess the components of physical fitness. Regarding physical function, it was verified that four studies applied specific tests to evaluate the activities of daily living. However, itwas observed in most of the studies that the physical aspects were only subjectively assessed through health-related quality of life questionnaires. Overall, all studies analysed showed that the health-related quality of life of sepsis survivors may be impaired after long periods of hospital discharge.
Source of funding	Not disclosed

Authors' conclusions	Most sepsis survivors presented impairments related to physical fitness and physical function after hospital discharge, as they showed impairments in their functional autonomy, resulting in loss of independence and autonomy in performing the activities of daily living.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	N
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	N
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	N
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	N
Overall quality	**Critically low**

Systematic review	**5**
Bibliographic reference	Calsavara AJC, Nobre V, Barichello T, Teixeira AL. Post-sepsis cognitive impairment and associated risk factors: A systematic review. Aust Crit Care. 2018;31(4):242–53.
Study type	Systematic review

Number of included trials	16
Search strategy	MEDLINE (1966 to March 2017) and EMBASE (1988 to March 2017).
Number of participants	>74 million people
Population	Adults with post-sepsis cognitive impairment
Intervention	Assessed cognitive dysfunction using objective measure
Comparison	Any comparator
Relevant outcome measures	Cognitive performance (measured)
Study designs	Case control, cohort and clinical trials
Outcomes	Significant variation was observed in the definition of sepsis and cognitive impairment. Twelve studies used ACCP/SCCM criteria for sepsis, while cognitive impairment was defined per test used. Post-sepsis cognitive impairment was observed in 12.5 to 21% of survivors of sepsis. Attention, cognitive flexibility, processing speed, associative learning, visual perception, work memory, verbal memory, and semantic memory were the specific domains affected. Depressive symptoms, central nervous system infection, length of hospitalisation due to infection, and temporal proximity to the last period of infection were associated with cognitive impairment.
Source of funding	No funding
Authors' conclusions	The studies are heterogeneous, and there is urgent need for a common language, including definitions and neuropsychological tests, for the investigation of post-sepsis cognitive impairment. Despite this, there is mounting evidence for the clinical relevance of post-sepsis cognitive impairment.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	N
Overall quality	**Low**

Systematic review	**6**
Bibliographic reference	Haas LE, van Dillen LS, de Lange DW, van Dijk D, Hamaker ME. Outcome of very old patients admitted to the ICU for sepsis: A systematic review. European Geriatric Medicine. 2017;8(5–6):446–53.
Study type	Systematic review
Number of included trials	18
Search strategy	Medline and Embase up to 2017
Number of participants	4,256 patients
Population	Adults aged > 80 years admitted to ICU with sepsis
Intervention	Any intervention
Comparison	Any comparator
Relevant outcome measures	ICU-, hospital-mortality and/or any other short- or long-term outcome measure; e.g. 30-day mortality or one-year mortality and also functional outcome and quality of life
Study designs	Observational (12 retrospective, 6 prospective)
Outcomes	The median ICU mortality was 43% [range 30–79%], the median hospital-mortality 47% [31–84%] and the median 1-year mortality 68% [53–83%].
Source of funding	Not funded
Authors' conclusions	Although relatively few studies are performed in very old patients admitted with sepsis, mortality rates seem to be high. Future studies are needed to identify factors that can predict survival and quality of life after discharge of very old patients in order to identify subgroups that benefit most from ICU treatment.
Comments	
Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	N
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	N
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**7**
Bibliographic reference	Haller S, Deindl P, Cassini A, Suetens C, Zingg W, Abu Sin M, et al. Neurological sequelae of healthcare-associated sepsis in very-low-birthweight infants: Umbrella review and evidence-based outcome tree. Euro Surveill. 2016;21(8):30143.
Study type	Meta-review
Number of included trials	Two systematic reviews (13 studies)
Search strategy	MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), without language restrictions from January 2000 to July 2014
Number of participants	6,092 patients
Population	Very low birthweight infants
Intervention	Sepsis acquired in a healthcare setting
Comparison	Participants without sepsis

Relevant outcome measures	Neurological outcomes
Study designs	Systematic reviews
Outcomes	The first systematic review included nine cohort studies with 5,620 participants and five outcomes (neurodevelopmental impairment, cerebral palsy, vision impairment, hearing impairment, death). Pooled risk differences varied between 4% (95% 2–10) and 13% (95% CI 5–20). From the second review we analysed four studies with 472 infants. Positive predictive value of neurodevelopmental impairment for later cognitive impairment ranged between 67% (95% CI:22–96) and 83% (95% CI:36–100).
Source of funding	European Centre for Disease Prevention and Control
Authors' conclusions	Neonatal sepsis increases risk of permanent neurological impairment.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Moderate**

Systematic review	8
Bibliographic reference	Huang J, Tang Y, Zhu T, Li Y, Chun H, Qu Y, et al. Cumulative evidence for association of sepsis and retinopathy of prematurity. Medicine (Baltimore). 2019;98(42):e17512.
Study type	Systematic review and meta-analysis
Number of included trials	34
Search strategy	PubMed, Embase, and Cochrane Library databases were searched to October 2018
Number of participants	Not described
Population	Preterm neonates (<37 weeks and birth weight <2,500g)
Intervention	Sepsis diagnosed by culture or clinical criteria
Comparison	No sepsis
Relevant outcome measures	Retinopathy of prematurity
Study designs	Case control
Outcomes	The pooled results showed that sepsis increased the risk for the development of any stage ROP (OR=2.16; 95% CI: 1.65–2.82). Both early onset (OR=2.50; 95% CI: 1.97–3.18) and late onset (OR=1.37; 95% CI: 1.22–1.55) sepsis were associated with severe ROP. Furthermore, both bacterial sepsis (OR=1.74; 95% CI: 1.21–2.50) and fungal sepsis (OR=2.96; 95% CI: 2.05–4.28) were also found to be associated with severe ROP.
Source of funding	This work was supported by the National Science Foundation of China (nos: 81630038, 81971433, 81971428, 81842011, 81330016, 81771634, 81300524), the National Key R&D Program of China (2017YFA0104200), the Grants from Ministry of Education of China (IRT0935), the Grants from Science and Technology Bureau of Sichuan Province (2016TD0002), and the grant of clinical discipline program (Neonatology) from the Ministry of Health of China (1311200003303).
Authors' conclusions	Sepsis increased the risk of any stage ROP, especially for the severe ROP. Further high-quality clinical studies are needed to eliminate heterogeneity and publication bias to validate these findings.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	N
6. Did the review authors perform data extraction in duplicate?	Y

7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Critically low**

Systematic review	9
Bibliographic reference	Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jette N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. Crit Care. 2015;19:139
Study type	Systematic review
Number of included trials	12
Search strategy	Embase and MEDLINE were searched for published articles to September 2014
Number of participants	Not reported in aggregate
Population	Hospital inpatients with sepsis, severe sepsis or septic shock
Intervention	International Classification of Diseases (ICD) 9 or 10 coded data used to define sepsis, severe sepsis or septic shock
Comparison	Reference standard (chart audit, ICU or surgical or bacteraemia database, sepsis clinical trial participants,
Relevant outcome measures	Sensitivity, specificity, positive and negative predictive values
Study designs	Observational health administration data
Outcomes	A total of 38 sepsis case definitions were tested, which included over 130 different ICD codes. The most common ICD-9 codes were 038.x, 790.7 and 995.92, and the most common ICD-10 codes were A40.x and A41.x. The PPV was reported in ten studies and ranged from 5.6% to 100%, with a median of 50%. Other tests of diagnostic accuracy were reported only in some studies. Sn ranged from 5.9% to 82.3%; Sp ranged from 78.3% to 100%; and NPV ranged from 62.1% to 99.7%.

Source of funding	Canadian Institutes of Health Research, Alberta Innovates: Health Solutions
Authors' conclusions	The validity of administrative data in recording sepsis varied substantially across individual studies and ICD definitions. Our work may serve as a reference point for consensus towards an improved and harmonized ICD-coded definition of sepsis.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	Partial Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**10**
Bibliographic reference	Menon K, McNally JD, Zimmerman JJ, Agus MS, O'Hearn K, Watson RS, et al. Primary outcome measures in pediatric septic shock trials: a systematic review. Pediatr Crit Care Med. 2017;18(3):e146-e54
Study type	Systematic review

Number of included trials	19
Search strategy	MEDLINE, EMBASE, LILACS and CENTRAL.
Number of participants	The median number of patients randomized was 60 (IQR 40, 121, range 27, 496)
Population	Children (median lower and upper age for included studies was 1 to 16 years) admitted to a paediatric intensive care unit (PICU) with septic or dengue haemorrhagic shock
Intervention	To evaluate all published paediatric randomized controlled trials (RCTs) of patients with septic shock from any cause to examine the outcome measures used, the strengths and limitations of these measurements and whether the trial outcomes met feasibility criteria.
Comparison	N/A
Relevant outcome measures	Mortality, duration of vasoactive-inotropic support, length of mechanical ventilation, organ dysfunction, PICU length of stay, hospital length of stay, or functional status or quality of life.
Study designs	RCTs
Outcomes	Fourteen of 19 studies (74%) provided an a priori definition of their primary outcome measure in their methods section. Mortality rate was the most commonly reported primary outcome (8/14, 57%), followed by duration of shock (4/14, 29%) followed by organ failure (1/14, 7%). Only 3 of 19 included trials met feasibility criteria.
Source of funding	Not funded
Authors' conclusions	Our review found that use of mortality alone as a primary outcome in paediatric septic shock trials was associated with significant limitations and that long-term patient centred outcomes were not utilized in this setting. Composite outcomes incorporating mortality and long-term outcomes should be explored for use in future paediatric septic shock trials.
Comments	The primary objective of this study was to describe the primary and secondary outcome measures reported in the included pediatric septic shock RCTs.

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	N/A
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N/A

10. Did the review authors report on the sources of funding included in the review?	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N/A
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**11**
Bibliographic reference	Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. Jama. 2018;319(1):62-75.
Study type	Systematic review
Number of included trials	Not described
Search strategy	Medline to April 2017
Number of participants	Not specified
Population	Not described
Intervention	Not defined
Comparison	Not defined
Relevant outcome measures	Not defined
Study designs	Not described
Outcomes	Each year, more than 19 million individuals develop sepsis, defined as a life- threatening acute organ dysfunction secondary to infection. Approximately 14 million survive to hospital discharge and their prognosis varies. Half of patients recover, one-third die during the following year, and one-sixth have severe persistent impairments. Impairments include development of an average of 1 to 2 new functional limitations (e.g., inability to bathe or dress independently), a 3-fold increase in prevalence of moderate to severe cognitive impairment (from 6.1% before hospitalisation to 16.7% after hospitalisation), and a high prevalence of mental health problems, including anxiety (32%of patients who survive), depression (29%), or posttraumatic stress disorder (44%). About 40% of patients are rehospitalised within 90 days of discharge, often for conditions that are potentially treatable in the outpatient setting, such as infection (11.9%) and exacerbation of heart failure (5.5%). Compared with patients hospitalised for other diagnoses, those who survive sepsis

	(11.9%) are at increased risk of recurrent infection than matched patients (8.0%) matched patients (P < .001), acute renal failure (3.3%vs 1.2%, P < .001), and new cardiovascular events (adjusted hazard ratio [HR] range, 1.1-1.4). Reasons for deterioration of health after sepsis are multifactorial and include accelerated progression of pre-existing chronic conditions, residual organ damage, and impaired immune function. Characteristics associated with complications after hospital discharge for sepsis treatment are not fully understood but include both poorer pre-sepsis health status, characteristics of the acute septic episode (e.g., severity of infection, host response to infection), and quality of hospital treatment (e.g., timeliness of initial sepsis care, avoidance of treatment-related harms). Although there is a paucity of clinical trial evidence to support specific post- discharge rehabilitation treatment, experts recommend referral to physical therapy to improve exercise capacity, strength, and independent completion of activities of daily living. This recommendation is supported by an observational study involving 30000 sepsis survivors that found that referral to rehabilitation within 90 days was associated with lower risk of 10-year mortality compared with propensity-matched controls (adjusted HR, 0.94; 95% CI, 0.92-0.97, P < .001).
Source of funding	K08 GM115859 (Dr Prescott) and R01 GM097471 (Dr Angus) from the National Institute of General Medical Sciences of the National Institutes of Health
Authors' conclusions	In the months after hospital discharge for sepsis, management should focus on (1) identifying new physical, mental, and cognitive problems and referring for appropriate treatment, (2) reviewing and adjusting long-term medications, and (3) evaluating for treatable conditions that commonly result in hospitalization, such as infection, heart failure, renal failure, and aspiration. For patients with poor or declining health prior to sepsis who experience further deterioration after sepsis, it may be appropriate to focus on palliation of symptoms.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	N
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	N
5. Did the authors perform study selection in duplicate?	N
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	N
8. Did the review authors describe the included studies in adequate detail?	N
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N
10. Did the review authors report on the sources of funding included in the review?	N

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Critically low**

Systematic review	**12**
Bibliographic reference	Robinson J, Swift-Scanlan T, Salyer J. Obesity and 1-Year Mortality in Adults After Sepsis: A Systematic Review. Biological research for nursing. 2020;22(1):103–13.
Study type	Systematic review
Number of included trials	9
Search strategy	PubMed, Cumulative Index of Nursing and Allied Health Literature, and Elton B. Stephens Company host databases were searched to May 2018
Number of participants	Over 1.8 million patients
Population	Subjects 18 years or older with sepsis
Intervention	Patients with obesity
Comparison	Patients with no obesity
Relevant outcome measures	Mortality
Study designs	Retrospective cohort studies
Outcomes	Three of the studies provide evidence to support the obesity paradox or the association of reduced mortality from sepsis in obese or very obese patients compared to nonobese patients. Of the remaining studies, five reported inconclusive results or conflicting evidence that there was no association between obesity and reduced short-term mortality from sepsis. In one study total ICU mortality in patients with sepsis was 22.5% with a mortality rate for nonobese patients of 21% and for obese patients 28.8% (p = .036).
Source of funding	Not funded

Authors' conclusions	This systematic review on the association of obesity and sepsis mortality found three studies that demonstrated lower sepsis mortality among obese patients in the first 30 days and one showing that this protective effect extends up to 1 year. Given the increased number of patients surviving sepsis, it is important to consider long term mortality and further describe the variables associated with increased survival.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	N
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	N
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Critically low**

Systematic review	**13**
Bibliographic reference	Shankar-Hari M, Ambler M, Mahalingasivam V, Jones A, Rowan K, Rubenfeld GD. Evidence for a causal link between sepsis and long-term mortality: a systematic review of epidemiologic studies. Crit Care. 2016;20:101.
Study type	Systematic review and meta-analysis

Number of included trials	59
Search strategy	Medline and Embase searched. Date of last search June 2015.
Number of participants	1.45 million patients
Population	Adult patients reporting an episode of sepsis using either the 1992 or 2003 consensus definitions
Intervention	Patients who died during follow-up
Comparison	Patients who survived
Relevant outcome measures	All-cause one year or longer mortality
Study designs	Not described in full
Outcomes	In patients who survived an index sepsis admission, the post-acute mortality was 16.1% (95% CI 14.1, 18.1%) with significant heterogeneity on random effects meta-analysis. In studies reporting non-sepsis control arm comparisons, sepsis was not consistently associated with a higher hazard ratio for post-acute mortality. The additional hazard associated with sepsis was greatest when compared to the general population. Older age, male sex, and presence of comorbidities were commonly reported independent predictors of post-acute mortality in sepsis survivors, challenging the causality relationship. Sensitivity analyses for post-acute mortality were consistent with primary analysis.
Source of funding	Not funded
Authors' conclusions	Epidemiologic criteria for a causal relationship between sepsis and post-acute mortality were not consistently observed. Additional epidemiologic studies with recent patient level data that address the pre-illness trajectory, confounding, and varying control groups are needed to estimate sepsis- attributable additional risk and modifiable risk factors to design interventional trials.
Comments	I2 measure of heterogeneity very high and precluded statistical pooling of results. The authors pooled results anyway.

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	N
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y

10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Critically low**

Systematic review	**14**
Bibliographic reference	Shankar-Hari M, Saha R, Wilson J, Prescott HC, Harrison D, Rowan K, et al. Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. Intensive Care Medicine. 2020;46(4):619–36.
Study type	Systematic review and meta-analysis
Number of included trials	56
Search strategy	MEDLINE, Cochrane Library, Web of Science, and EMBASE from 1992 to October 2019.
Number of participants	6.7 million patient episodes (36 full studies)
Population	Patients surviving hospital admission for sepsis or septic shock
Intervention	Any intervention
Comparison	Any comparator
Relevant outcome measures	Re-hospitalisation (all cause)
Study designs	Non-randomised studies (36 full text and 20 conference abstracts)
Outcomes	Studies most often report 30-day rehospitalisation rate (mean 21.4%, 95% confidence interval [CI] 17.6–25.4%; N = 36 studies reporting 6,729,617 patients). The mean (95%CI) rehospitalisation rates increased from 9.3% (8.3–10.3%) by 7 days to 39.0% (22.0–59.4%) by 365 days. Infection was the most common rehospitalisation diagnosis. Risk factors that increased the rehospitalisation risk in sepsis survivors were generic characteristics such as older age, male, comorbidities, non-elective admissions, hospitalisation prior to index sepsis admission, and sepsis characteristics such as infection and illness severity, with hospital characteristics showing inconsistent associations. The overall certainty of evidence was moderate for rehospitalisation rates and low for risk factors.

Source of funding	National Institute for Health Research
Authors' conclusions	Rehospitalisation events are common in sepsis survivors, with one in five rehospitalisation events occurring within 30 days of hospital discharge following an index sepsis admission. The generic and sepsis-specific characteristics at index sepsis admission are commonly reported risk factors for rehospitalisation.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**15**
Bibliographic reference	Taito S, Taito M, Banno M, Tsujimoto H, Kataoka Y, Tsujimoto Y. Rehabilitation for patients with sepsis: A systematic review and meta-analysis. PLoS ONE. 2018;13(7):e0201292.
Study type	Systematic review and meta-analysis

Number of included trials	2
Search strategy	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PEDro, and the World Health Organization International Clinical Trials Platform Search Portal, as well as conference proceedings and reference lists of relevant articles. Last search May 2018.
Number of participants	75
Population	Adult patients with sepsis
Intervention	Rehabilitation intervention
Comparison	Usual care, no intervention
Relevant outcome measures	Quality of life (QOL), activity of daily living (ADL), and mortality, length of stay, return to work, muscle strength, delirium, and all adverse events.
Study designs	RCTs
Outcomes	The mean difference (95% confidence interval [CI]) of physical function and physical role in QOL measured by SF-36 were 21.10 (95% CI: 6.57–35.63) and 44.40 (95% CI: 22.55–66.05), respectively. Rehabilitation did not significantly decrease intensive care unit (ICU) mortality (risk ratio, 2.02 [95% CI: 0.46–8.91], I2 = 0%; n = 75). ICU length of stay and hospital length of stay and muscle strength were not statistically significantly different and no adverse events were reported in both studies. The certainty of the evidence for these outcomes was “very low.” Data on ADL, return to work, and delirium were not available in any of the trials.
Source of funding	JSPS KAKENHI Grant Number JP18K17719.
Authors’ conclusions	Rehabilitation of patients with sepsis might not decrease ICU mortality, but might improve QOL. Further, well-designed trials measuring important outcomes will be needed to determine the benefit and harm of rehabilitation among patients with sepsis.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**High**

Systematic review	**16**
Bibliographic reference	Tsertsvadze A, Royle P, Seedat F, Cooper J, Crosby R, McCarthy N. Community-onset sepsis and its public health burden: a systematic review. Syst. 2016;5:81.
Study type	Systematic review
Number of included trials	14
Search strategy	Medline and Embase databases were searched from 2002 to May 20References of relevant publications were hand-searched.
Number of participants	Not described in full
Population	Community dwellers, hospitalised patients (male/female) of any age (except for neonates) from a defined population with or without community onset sepsis (COS) at study baseline.
Intervention	Any patient characteristic or clinical parameter (e.g., age, sex, co-morbidity, heart rate, body temperature) associated with a risk of COS
Comparison	N/A
Relevant outcome measures	Annual incidence of community onset sepsis, risk factors for COS
Study designs	Cohort (10) and case control (4) studies
Outcomes	There was a wide variation in the incidence (# cases per 100,000 per year) of non-severe sepsis (range: 64–514), severe sepsis (range: 40–455), and septic shock (range: 9–31). Heterogeneity precluded statistical pooling.

	Two cohort and 4 case-control studies reported risk factors for sepsis. In one case-control and one cohort study, older age and diabetes were associated with increased risk of sepsis. The same case-control study showed an excess risk for sepsis in participants with clinical conditions (e.g., immunosuppression, lung disease, and peripheral artery disease). In one cohort study, higher risk of sepsis was associated with being a nursing home resident (OR = 2.60, 95 % CI: 1.20, 5.60) and in the other cohort study with being physically inactive (OR = 1.33, 95 % CI: 1.13, 1.56) and smoking tobacco (OR = 1.85, 95 % CI: 1.54, 2.22). The evidence on sex, ethnicity, statin use, and body mass index as risk factors was inconclusive.
Source of funding	Public Health England
Authors' conclusions	The lack of a valid standard approach for defining sepsis makes it difficult to determine the true incidence of COS. Differences in case ascertainment contribute to the variation in incidence of COS. The evidence on COS is limited in terms of the number and quality of studies. This review highlights the urgent need for an accurate and standard method for identifying sepsis. Future studies need to improve the methodological shortcomings of previous research in terms of case definition, identification, and surveillance practice.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y

15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Moderate**

Systematic review	**17**
Bibliographic reference	Vallabhajosyula S, Rayes HA, Sakhuja A, Murad MH, Geske JB, Jentzer JC. Global Longitudinal Strain Using Speckle-Tracking Echocardiography as a Mortality Predictor in Sepsis: A Systematic Review. J Intensive Care Med. 2019;34(2):87–93.
Study type	Systematic review
Number of included trials	5
Search strategy	PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, Embase, Scopus, and Web of Science databases from January 1975 to December 31, 2016
Number of participants	561 participants
Population	Adults and children with sepsis, severe sepsis or septic shock
Intervention	Patients with global longitudinal strain (GLS) of the heart diagnosed with speckle-tracking echocardiography (STE)
Comparison	Patients without global longitudinal strain
Relevant outcome measures	Mortality
Study designs	Prospective observational
Outcomes	Three studies demonstrated worse systolic GLS to be associated with higher mortality, whereas 2 did not show a statistically significant association. Various cutoffs between -10% and -17% were used to define abnormal GLS across studies.
Source of funding	Not funded
Authors' conclusions	This systematic review revealed that STE may predict mortality in patients with sepsis; however, the strength of evidence is low due to heterogeneity in study populations, GLS technologies, cutoffs, and timing of STE. Further dedicated studies are needed to understand the optimal application of STE in patients with sepsis.
Comments	
Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y

4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Systematic review	**18**
Bibliographic reference	Wang X, Tang K, Chen L, Cheng S, Xu H. Association between sepsis and retinopathy of prematurity: a systematic review and meta-analysis. BMJ Open. 2019;9(5):e025440.
Study type	Systematic review and meta-analysis
Number of included trials	16
Search strategy	PubMed, the Cochrane Library and Embase from 1 January 2000, to 1 January, 2018
Number of participants	12,466 premature infants (comprising 2,494 cases of retinopathy of prematurity)
Population	Infants <37 weeks gestation at birth with sepsis diagnosis
Intervention	Sepsis diagnosis
Comparison	No sepsis diagnosis
Relevant outcome measures	Retinopathy of prematurity based on ophthalmoscopic examination performed by ophthalmologist or neonatologist
Study designs	Observational studies

Outcomes	Adjusted analysis showed that sepsis was closely related to any stage of ROP (OR = 1.57, 95% CI 1.31 to 1.89) and severe stage of ROP (OR = 2.33, 95% CI 1.21 to 4.51) in premature infants, with 56.3% and 81.8% heterogeneity, respectively. Subgroup analyses showed that heterogeneity was obvious in prospective cohort studies (I2 = 62.1%, p<0.001). In a sensitivity analysis, we found that removing any single study did not significantly change the overall effect value. The quality of the evidence was rated as low for both any stage of ROP and severe stage of ROP.
Source of funding	Not funded
Authors' conclusions	Sepsis increases the risk of ROP in preterm infants. However, considering that all included studies are observational and causality can rarely be established, additional evidence is needed to substantiate this finding and provide advice for practice.
Comments	

Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Moderate**

Systematic review	19
Bibliographic reference	Wang Z, Ren J, Wang G, Liu Q, Guo K, Li J. Association between diabetes mellitus and outcomes of patients with sepsis: a meta-analysis. Med Sci Monit. 2017;23:3546-55.
Study type	Systematic review and meta-analysis
Number of included trials	10
Search strategy	PubMed, Embase, and Cochrane Library databases from 1966 to July 1, 2016
Number of participants	261,342 patients
Population	Adult patients with sepsis
Intervention	Patients with diabetes
Comparison	Patients with no diabetes
Relevant outcome measures	Mortality, length of hospital stay, the incidence of acute kidney injury (AKI), and respiratory dysfunction
Study designs	Cohort studies (5 prospective, 5 retrospective)
Outcomes	Mortality rate of septic patients with DM was slightly lower than that of non- diabetic patients (RR 0.97, 95% CI 0.96 to 0.98). Septic patients with DM had a shorter hospital stay (WMD –2.27, 95% CI –4.11 to –0.44), a higher incidence rate of AKI (RR 1.56, 95% CI 1.25 to 1.95) and a similar incidence of respiratory dysfunction (RR 0.86, 95% CI 0.71 to 1.04) compared with those without DM.
Source of funding	Not disclosed
Authors' conclusions	DM does not impair the outcome of patients with sepsis, and the incidence of acute kidney injury increases dramatically in septic patients with DM. Due to the limitations of the analysis, more well-designed trials are still necessary.
Comments	
Quality appraisal (AMSTAR 2)	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N
3. Did the authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the authors use a comprehensive literature search strategy?	Y
5. Did the authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	N
7. Did the authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding included in the review?	N

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding the received for conducting the review?	Y
Overall quality	**Low**

Randomised controlled trials

RCT	1
Bibliographic reference	Schmidt KF, Schwarzkopf D, Baldwin LM, Brunkhorst FM, Freytag A, Heintze C, et al. Long-term courses of sepsis survivors: effects of a primary care management intervention. Am J Med. 2020;133(3):381-5.e5.
Study type	Randomised controlled trial
Number of participants	291 participants – 186 completed 24-month follow-up
Population	Adults treated for sepsis in German ICU
Intervention	12-month primary care intervention. Evidence-based post-sepsis care, case management provided by trained nurses, and clinical decision support for primary care physicians by consulting physicians
Comparison	Usual care
Relevant outcome measures	Mortality, SF-36 measures
Outcomes	At 24 months, there was no difference between groups in the Mental Component Summary of the 36-Item Short Form Health Survey (SF-36). Differences between the two groups in Activities of Daily Living, motor function, and sleep quality identified in the 6 and 12-month follow-up periods did not persist to 24 months. Patients in the control group experienced significantly more symptoms of post-traumatic stress disorder than the intervention group.
Source of funding	Center for Sepsis Control & Care, funded by the German Ministry of Education and Research (BMBF), grant no. 01 E0 1002.
Authors' conclusions	One year after termination of a primary care management intervention (24 months after discharge from the ICU) there was no evidence of improved mental health-related quality of life or physical function among survivors of sepsis. An increase in late-onset PTSD symptoms in the control group suggests a possible protective effect of the intervention. More research is needed to understand late-onset PTSD in patients who survive sepsis and to generate options for its prevention.
Comments	
Quality appraisal (Cochrane Risk of Bias)	
Random sequence generation (selection bias)	Low
Allocation concealment (selection bias)	Low
Blinding of participants and personnel (performance bias)	High
Blinding of outcome assessment (detection bias)	High
Incomplete outcome data (attrition bias)	High
Selective reporting (reporting bias)	Low
Other bias	Low
Overall quality	**High**

RCT	2
Bibliographic reference	Higgins AM, Peake SL, Bellomo R, Cooper DJ, Delaney A, Harris AH, et al. Quality of life and 1-year survival in patients with early septic shock: long-term follow-up of the Australasian resuscitation in sepsis evaluation trial. Crit Care Med. 2019;47(6):765-773.
Study type	Randomised controlled trial
Number of participants	1,591 patients
Population	Patients presenting to ED with early septic shock between October 2008 and April 2014 and enrolled in the Australasian Resuscitation in Sepsis Evaluation trial
Intervention	Early goal directed therapy
Comparison	Usual care
Relevant outcome measures	12-month mortality, health-related quality of life
Outcomes	Mortality data were available for 1,548 patients (97.3%) and 1,515 patients (95.2%) at 6 and 12 months, respectively. Health-related quality of life data were available for 85.1% of survivors at 12 months. There were no significant differences in mortality between groups at either 6 months (early goal- directed therapy 21.8% vs usual care 22.6%; p = 0.70) or 12 months (early goal-directed therapy 26.4% vs usual care 27.9%; p = 0.50). There were no group differences in health-related quality of life at either 6 or 12 months (EuroQoL-5D-3L utility scores at 12 months early goal-directed therapy 0.65 ± 0.33 vs usual care 0.64 ± 0.34; p = 0.50), with the health-related quality of life of both groups being significantly lower than population norms.
Source of funding	National Health and Medical Research Council
Authors' conclusions	In patients presenting to the emergency department with early septic shock, early goal-directed therapy compared with usual care did not reduce mortality nor improve health-related quality of life at either 6 or 12 months.
Comments	
Quality appraisal (Cochrane Risk of Bias)	
Random sequence generation (selection bias)	Low
Allocation concealment (selection bias)	Low
Blinding of participants and personnel (performance bias)	High
Blinding of outcome assessment (detection bias)	High
Incomplete outcome data (attrition bias)	Low
Selective reporting (reporting bias)	Low
Other bias	Low
Overall quality	**Low**

Non-randomised studies

Non-randomised studies	1
Bibliographic reference	Gardner AK, Ghita GL, Wang Z, Ozrazgat-Baslanti T, Raymond SL, Mankowski RT, et al. The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. Crit Care Med. 2019;47(4):566-73.
Study type	Prospective cohort study
Number of participants	The cohort consisted of 173 sepsis patients; 63 (36%) developed chronic critical illness and 110 (64%) exhibited rapid recovery.
Population	Adult critically ill patients that survived 14 days or longer after sepsis onset.
Methods	Baseline patient characteristics and function, sepsis severity, and clinical outcomes of the index hospitalization were collected. Follow-up physical function (short physical performance battery; Zubrod; hand grip strength) and health-related quality of life (EuroQol-5D-3L, Short Form-36) were measured at 3, 6, and 12 months. Hospital-free days and mortality were determined at 12 months. We compared differences in long-term outcomes between subjects who developed chronic critical illness (≥ 14 ICU days with persistent organ dysfunction) versus those with rapid recovery.
Results	Baseline physical function and health-related quality of life did not differ between groups. Those who developed chronic critical illness had significantly fewer hospital-free days (196 ± 148 vs 321 ± 65; $p < 0.0001$) and reduced survival at 12-months compared with rapid recovery subjects (54% vs 92%; $p < 0.0001$). At 3- and 6-month follow-up, chronic critical illness patients had significantly lower physical function (3 months: short physical performance battery, Zubrod, and hand grip; 6 months: short physical performance battery, Zubrod) and health-related quality of life (3- and 6-mo: EuroQol-5D-3L) compared with patients who rapidly recovered. By 12-month follow-up, chronic critical illness patients had significantly lower physical function and health-related quality of life on all measures.
Source of funding	
Authors' conclusions	Surgical patients who develop chronic critical illness after sepsis exhibit high healthcare resource utilization and ultimately suffer dismal long-term clinical, functional, and health-related quality of life outcomes. Further understanding of the mechanisms driving the development and persistence of chronic critical illness will be necessary to improve long-term outcomes after sepsis.
Comments	

Quality appraisal (Newcastle-Ottawa Scale	Score
Representativeness of the exposed cohort	0
Selection of the non-exposed cohort	1
Ascertainment of exposure	1
Demonstration the outcome of interest was not present at the start of the study	1
Comparability of cohorts on the basis of design or analysis	1
Assessment of outcome	0
Follow-up long enough for outcomes to occur	0
Adequacy of follow up of cohorts	0

Overall quality	Poor

Non-randomised studies	2
Bibliographic reference	Mankowski RT, Anton SD, Ghita GL, Brumback B, Cox MC, Mohr AM, et al. Older sepsis survivors suffer persistent disability burden and poor long-term survival. J Am Geriatr Soc. 2020.
Study type	Prospective cohort study
Number of participants	328 patients
Population	Adult surgical intensive care unit (ICU) sepsis patients.
Methods	Patients were characterized by (1) baseline demographics and predisposition, (2) septic event, (3) hospital outcomes and discharge disposition, (4) 12- month mortality, and (5) Zubrod Performance Status, physical function (Short Physical Performance Battery and handgrip strength), and cognitive function (Hopkins Verbal Learning Test, Controlled Oral Word Association, and Mini- Mental Status Examination) at 3-, 6-, and 12-month follow-up. Loss to follow-up was due to death (in 68), consent withdrawal (in 32), and illness and scheduling difficulties: month 3 (in 51), month 6 (in 29), and month 12 (in 20).
Results	Compared with young and middle-aged patients, older patients had (1) significantly more comorbidities at presentation (eg, chronic renal disease 6% vs 12% vs 21%), intra-abdominal infections (14% vs 25% vs 37%), septic shock (12% vs 25% vs 36%), and organ dysfunctions; (2) higher 30-day mortality (6% vs 4% vs 17%) and fewer ICU-free days (median = 25 vs 23 vs 20); (3) more progression into chronic critical illness (22% vs 34% vs 42%) with higher poor disposition discharge to non-home destinations (19% vs 40% vs 62%); (4) worse 12-month mortality (11% vs 14% vs 33%); and (5) poorer Zubrod Performance Status and objectively measured physical and cognitive functions with only slight improvement over 12-month follow-up.
Source of funding	US National Institute of General Medical Sciences (NIGMS)
Authors' conclusions	Compared with younger patients, older sepsis survivors suffer both a higher persistent disability burden and 12-month mortality.
Comments	

Quality appraisal (Newcastle-Ottawa Scale	Score
Representativeness of the exposed cohort	0
Selection of the non-exposed cohort	1
Ascertainment of exposure	1
Demonstration the outcome of interest was not present at the start of the study	1
Comparability of cohorts on the basis of design or analysis	1
Assessment of outcome	1
Follow-up long enough for outcomes to occur	0
Adequacy of follow up of cohorts	0
Overall quality	**Fair**

Non-randomised studies	3
Bibliographic reference	Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, Shah NH, et al. The impact of acute organ dysfunction on long-term survival in sepsis. Critical Care Medicine. 2018;46(6):843-9.
Study type	Retrospective cohort study
Number of participants	30,163 patients
Population	Sepsis patients admitted through the emergency department between 2010 and 2013, with mortality follow-up through April 2015.
Methods	21 hospitals within an integrated healthcare delivery system in Northern California. Acute organ dysfunction was quantified using modified Sequential Organ Failure Assessment scores. The main outcome was long-term mortality among sepsis patients who survived hospitalization. The estimates of the impact of each type of acute organ dysfunction on long-term mortality were based on adjusted Cox proportional hazards models. Sensitivity analyses were conducted based on propensity score-matching and adjusted logistic regression.
Results	Hospital mortality was 9.4% and mortality was 31.7% at 1 year. Median follow-up time among sepsis survivors was 797 days (interquartile range: 384–1,219 d). Acute neurologic (odds ratio, 1.86; $p < 0.001$), respiratory (odds ratio, 1.43; $p < 0.001$), and cardiac (odds ratio, 1.31; $p < 0.001$) dysfunction were most strongly associated with short-term hospital mortality, compared with sepsis patients without these organ dysfunctions. Evaluating only patients surviving their sepsis hospitalization, acute neurologic dysfunction was also most strongly associated with long-term mortality (odds ratio, 1.52; $p < 0.001$) corresponding to a marginal increase in predicted 1-year mortality of 6.0% for the presence of any neurologic dysfunction ($p < 0.001$). Liver dysfunction was also associated with long-term mortality in all models, whereas the association for other organ dysfunction subtypes was inconsistent between models.
Source of funding	US National Institute of General Medical Sciences and National Institutes of Health
Authors' conclusions	Acute sepsis-related neurologic dysfunction was the organ dysfunction most strongly associated with short-and long-term mortality and represents a key mediator of long-term adverse outcomes following sepsis.
Comments	

Quality appraisal (Newcastle-Ottawa Scale	Score
Representativeness of the exposed cohort	0
Selection of the non-exposed cohort	1
Ascertainment of exposure	1
Demonstration the outcome of interest was not present at the start of the study	1
Comparability of cohorts on the basis of design or analysis	2
Assessment of outcome	1
Follow-up long enough for outcomes to occur	0

Adequacy of follow up of cohorts	1
Overall quality	**Good**

Non-randomised studies	**4**
Bibliographic reference	Shankar-Hari M, Harrison DA, Ferrando-Vivas P, Rubenfeld GD, Rowan K. Risk factors at index hospitalization associated with longer-term mortality in adult sepsis survivors. JAMA Network Open. 2019;2(5).
Study type	Cohort study
Number of participants	94,748 patients
Population	Adult sepsis survivors
Methods	This cohort study included a nationally representative sample of patients from 192 critical care units in England. Participants were identified from consecutive critical care admissions between April 1, 2009, and March 31, 2014, with survival status ascertained as of March 31, 2015. Statistical analyses were completed in June 2017. EXPOSURES Generic patient characteristics (age, sex, ethnicity, severe comorbidities [defined using the Acute Physiology and Chronic Health Evaluation II method], dependency, surgical status, and acute illness severity [scored using the Acute Physiology and Chronic Health Evaluation II acute physiology component]) and sepsis- specific patient characteristics (site of infection, number of organ dysfunctions, and septic shock status) known during index critical care admission for sepsis. Long-term mortality in adult sepsis survivors with maximum follow-up of 6 years. Adjusted hazard ratios (HRs) were estimated using Cox regression for both generic and sepsis-specific patient characteristics.
Results	Sepsis survivors had a mean (SD) age of 61.3 (17.0) years, 43 584 (46.0%) were female, and 86 056 (90.8%) were white. A total of 46.3%had respiratory site of infection. By 1 year from hospital discharge, 15%of sepsis survivors had died, with 6% to 8% dying per year over the subsequent 5 years. Age, sex, race/ethnicity, severe comorbidities, dependency, nonsurgical status, and site of infection were independently associated with long-term mortality. Compared with single organ dysfunction, having 2 or 3 organ dysfunctions was associated with increased risk of long-term mortality (adjusted HR, 1.07; 95%CI, 1.01–1.13; and adjusted HR, 1.18; 95%CI, 1.03–1.14, respectively), while having 4 organ dysfunctions or more was not associated with increased risk. Unexpectedly, the Acute Physiology and Chronic Health Evaluation acute physiology component score had an incremental association with long- term mortality (adjusted HR, 1.11 for every 5-point increase; 95% CI, 1.08–1.13). The adjusted HR for septic shock was 0.89 (95%CI, 0.85–0.92).
Source of funding	National Institute for Health Research Clinician Scientist Award CS-2016-16- 011.
Authors' conclusions	This study suggests that generic and sepsis-specific risk factors, known during index critical care admission for sepsis, could identify a high-risk sepsis survivor population for biological characterization and designing interventions to reduce long-term mortality.

Comments	

Quality appraisal (Newcastle-Ottawa Scale	Score
Representativeness of the exposed cohort	1
Selection of the non-exposed cohort	1
Ascertainment of exposure	1
Demonstration the outcome of interest was not present at the start of the study	1
Comparability of cohorts on the basis of design or analysis	2
Assessment of outcome	1
Follow-up long enough for outcomes to occur	0
Adequacy of follow up of cohorts	1
Overall quality	**Good**

Non-randomised studies	5
Bibliographic reference	Su YX, Xu L, Gao XJ, Wang ZY, Lu X, Yin CF. Long-term quality of life after sepsis and predictors of quality of life in survivors with sepsis. Chin J Traumatol. 2018;21(4):216-23
Study type	Prospective case-control study
Number of participants	612 participants
Population	Adult survivors of sepsis
Methods	Screened intensive care unit (ICU) patients in Tianjin Third Central Hospital from January 2014 to October 2017, and the Chinese general population in the previous studies was also included. According to inclusion criteria and exclusion criteria, 306 patients with sepsis were enrolled as the observation group, and another 306 patients without sepsis in ICU during the same period, whose ages, gender and Charlson Comorbidity Index matched with observation group, were enrolled as the control group. At 3 months, 12 months, and 24 months after discharge, the 36-item Short Form Health Survey (SF-36), the Euroqol-5 dimension (EQ-5D), and the activities of daily living (ADL) were evaluated in face-to-face for the quality of life among survivors.

Results	There were 210 (68.6%) septic patients and 236 (77.1%) non-septic critically ill patients surviving. At 3 months after discharge, the observation and control groups had the similar demographic characteristics (age: 58.8 ± 18.1years vs. 57.5 ± 17.6 years, p = 0.542; male: 52.0% vs. 51.4%, p = 0.926). However, the observation group had higher acute physiology and chronic health evaluation II (APACHEII) scores, higher sequential organ failure assessment (SOFA) scores, longer hospital stay, and longer ICU stay than the control group did (p < 0.05). There were no significant differences in the eight dimensions of the SF36 scale, the EQ-5D health utility scores, and the activities of daily life scores between septic survivors and non-septic survivors (p > 0.05). In addition, compared with the quality of life of the Chinese general population (aged 55–64 years), the quality of life of septic patients were significantly lower at 3 months after discharge (p < 0.05). Comparing the quality of life of the ill patients who had been discharged at 3 mo and 24 mo, the general health improved statistically (p = 0.000) and clinically (score improvement > 5 points). Older age (OR, 1.050; 95% CI, 1.022–1.078, p = 0.000), female (OR, 3.375; 95% CI, 1.434–7.941, p = 0.005) and longer mechanical ventilation time (OR, 3.412; 95% CI, 1.413, 8.244, p = 0.006) were the risk factors for the quality of life of septic survivors.
Source of funding	Health and Family Planning Commission Technology Fund of Tianjin (20152D-GG-xulei).
Authors' conclusions	The long-term quality of life of septic survivors was similar to that of non-sepsis critically ill survivors. After discharge, the general health of sepsis improved overtime. Age, female and mechanical ventilation time (>5 days) were the predictors of the quality of life after sepsis.
Comments	

Quality appraisal (Newcastle-Ottawa Scale	**Score**
Representativeness of the exposed cohort	0
Selection of the non-exposed cohort	0
Ascertainment of exposure	1
Demonstration the outcome of interest was not present at the start of the study	0
Comparability of cohorts on the basis of design or analysis	1
Assessment of outcome	0
Follow-up long enough for outcomes to occur	1
Adequacy of follow up of cohorts	0
Overall quality	**Poor**

Other studies

Other	1
Bibliographic reference	Buchman TG, Simpson SQ, Sciarretta KL, Finne KP, Sowers N, Collier M, et al. Sepsis among Medicare beneficiaries: 2. The trajectories of sepsis, 2012–2018. Crit Care Med. 2020;48(3):289-301.
Study design	Analysis of paid Medicare claims via the Centers for Medicare and Medicaid Services DataLink Project.
Methods	Analysis of linked administrative data. All U.S. acute care hospitals, excepting federal hospitals (Veterans Administration and Defense Health Agency). Medicare beneficiaries, 2012–2018, with an inpatient hospital admission including one or more explicit sepsis codes.
Results	Prevalent diagnoses in the year prior to the inpatient admission; healthcare contacts in the week prior to the inpatient admission; discharges, transfers, readmissions, and deaths (trajectories) for 6 months following discharge from the inpatient admission. Beneficiaries with no sepsis inpatient hospital admission for a year prior to an index hospital admission for sepsis were nearly indistinguishable by accumulated diagnostic codes from beneficiaries who had an index hospital admission without sepsis. Although the timing of healthcare services in the week prior to inpatient hospital admission was similar among beneficiaries who would be admitted for sepsis versus those whose inpatient admission did not include a sepsis code, the setting differed: beneficiaries destined for a sepsis admission were more likely to have received skilled nursing or unskilled nursing (e.g., nursing aide for activities of daily living) care. In contrast, comparing beneficiaries who had been free of any inpatient admission for an entire year and then required an inpatient admission, acute inpatient stays that included a sepsis code led to more than three times as many deaths within 1 week of discharge, with more admissions to skilled nursing facilities and fewer discharges to home. Comparing all beneficiaries who were admitted to a skilled nursing facility after an inpatient hospital admission, those who had sepsis coded during the index admission were more likely to die in the skilled nursing facility; more likely to be readmitted to an acute inpatient hospital and subsequently die in that setting; or if they survive to discharge from the skilled nursing facility, they are more likely to go next to a custodial nursing home.
Source of funding	US Government
Authors' conclusions	Although Medicare beneficiaries destined for an inpatient hospital admission with a sepsis code are nearly indistinguishable by other diagnostic codes from those whose admissions will not have a sepsis code, their healthcare trajectories following the admission are worse. This suggests that an inpatient stay that included a sepsis code not only identifies beneficiaries who were less resilient to infection but also signals increased risk for worsening health, for mortality, and for increased use of advanced healthcare services during and post discharge along with an increased likelihood of an inpatient hospital readmission.
Comments	

Other	2
Bibliographic reference	Ehlenbach WJ, Gilmore-Bykovskyi A, Repplinger MD, Westergaard RP, Jacobs EA, Kind AJ, et al. Sepsis survivors admitted to skilled nursing facilities: cognitive impairment, activities of daily living dependence, and survival. Crit Care Med. 2018;46(1):37-44.
Study design	Analysis of linked administrative hospital data collection from Medicare beneficiaries
Methods	Data analysed for random 5% sample of Medicare patients discharged following severe sepsis hospitalization, 2005–2009 (n = 135,370) fro US hospitals. Medicare data were linked with the Minimum Data Set; Minimum Data Set-Cognition Scale was used to assess cognitive function, and the Minimum Data Set activities of daily living hierarchical scale was used to assess functional dependence. Associations were evaluated using multivariable logistic regression, Kaplan-Meier curves, and Cox proportional hazards regression.
Results	Of 66,540 beneficiaries admitted to a skilled nursing facility following severe sepsis, 34% had severe or very severe cognitive impairment, and 72.5% had maximal, dependence, or total dependence in activities of daily living. Median survival was 19.4 months for those discharged to a skilled nursing facility without having been in a skilled nursing facility in the preceding 1 year and 10.4 months for those discharged to a skilled nursing facility who had spent time in a skilled nursing facility in the prior year. The adjusted hazard ratio for death was 3.1 for those with very severe cognitive impairment relative to those who were cognitively intact (95% CI, 2.9–3.2; $p < 0.001$) and 4.3 for those with "total dependence" in activities of daily livings relative to those who were independent (95% CI, 3.8–5.0; $p < 0.001$).
Source of funding	
Authors' conclusions	Discharge to a skilled nursing facility following severe sepsis hospitalization among Medicare beneficiaries was associated with shorter survival, and cognitive impairment and activities of daily living dependence were each strongly associated with shortened survival. These findings can inform decision-making by patients and physicians and underscores high palliative care needs among sepsis survivors discharged to skilled nursing facility.
Comments	

Other	3
Bibliographic reference	Konig C, Matt B, Kortgen A, Turnbull AE, Hartog CS. What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. Quality of Life Research. 2019;28(3):637-47.
Study design	Qualitative study
Methods	A literature search was performed to inform an interview guide. Open-ended interviews were held with 15 purposefully sampled sepsis survivors. Interview transcripts were analysed by interpretative phenomenological analysis to allow themes to develop organically. Resulting codes were reviewed by an independent expert. The preliminary list of domains was rated in a two-round Delphi consensus procedure with therapists and survivors.

Results	Eleven domains emerged as critically important: Psychological impairment, Fatigue, Physical impairment, Coping with daily life, Return to normal living, Ability to walk, Cognitive impairment, Self-perception, Control over one's life, Family support, and Delivery of health care. Sepsis survivors want a "normal life," to walk again, and to regain control without cognitive impairment. Family support is essential to overcome sepsis aftermaths.
Source of funding	
Authors' conclusions	Survivors described many HRQL domains which are not captured by the QoL instruments that have traditionally been used to study ICU survivorship (i.e., SF-36 and EQ-5D). Future studies of QoL in ICU survivors should consider using both a traditional instrument so that results are comparable to previous research, as well as a more holistic QoL measurement instrument like the WHOQOL-BREF.
Comments	

Other	**4**
Bibliographic reference	Prescott HC, Iwashyna TJ, Blackwood B, Calandra T, Chlan LL, Choong K, et al. Understanding and enhancing sepsis survivorship. priorities for research and practice. Am J Respir Crit Care Med. 2019;200(8):972-81.
Study design	International consensus meeting
Methods	International Sepsis Forum convened a colloquium in February 2018 titled "Understanding and Enhancing Sepsis Survivorship." The goals were to identify gaps and limitations of current research and shorter- and longer-term priorities for understanding and enhancing sepsis survivorship. 26 experts from eight countries participated.
Results	The top short-term priorities identified by nominal group technique culminating in formal voting were to better leverage existing databases for research, develop and disseminate educational resources on post-sepsis morbidity, and partner with sepsis survivors to define and achieve research priorities. The top longer-term priorities were to study mechanisms of long-term morbidity through large cohort studies with deep phenotyping, build a harmonized global sepsis registry to facilitate enrolment in cohorts and trials, and complete detailed longitudinal follow-up to characterize the diversity of recovery experiences.
Source of funding	Canadian Critical Care Conference
Authors' conclusions	This perspective reviews colloquium discussions, the identified priorities, and current initiatives to address them.
Comments	

Other	**5**
Bibliographic reference	Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395(10219):200–11.
Study design	Global burden of disease study

Methods	We used multiple cause-of-death data from 109 million individual death records to calculate mortality related to sepsis among each of the 282 underlying causes of death in GBD 2017. The percentage of sepsis-related deaths by underlying GBD cause in each location worldwide was modelled using mixed-effects linear regression. Sepsis-related mortality for each age group, sex, location, GBD cause, and year (1990–2017) was estimated by applying modelled cause-specific fractions to GBD 2017 cause-of-death estimates. We used data for 8·7 million individual hospital records to calculate in-hospital sepsis-associated case-fatality, stratified by underlying GBD cause. In-hospital sepsis-associated case-fatality was modelled for each location using linear regression, and sepsis incidence was estimated by applying modelled case-fatality to sepsis-related mortality estimates.
Results	In 2017, an estimated 48·9 million (95% uncertainty interval [UI] 38·9–62·9) incident cases of sepsis were recorded worldwide and 11·0 million (10·1– 12·0) sepsis-related deaths were reported, representing 19·7% (18·2–21·4) of all global deaths. Age-standardised sepsis incidence fell by 37·0% (95% UI 11·8–54·5) and mortality decreased by 52·8% (47·7–57·5) from 1990 to 2017. Sepsis incidence and mortality varied substantially across regions, with the highest burden in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia.
Source of funding	The Bill & Melinda Gates Foundation, the National Institutes of Health, the University of Pittsburgh, the British Columbia Children's Hospital Foundation, the Wellcome Trust, and the Fleming Fund.
Authors' conclusions	Despite declining age-standardised incidence and mortality, sepsis remains a major cause of health loss worldwide and has an especially high health- related burden in sub-Saharan Africa.
Comments	

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