UK National Surgical Research Collaborative, Trickey, A., & McNair, A. (2017). Multicentre observational study of adherence to Sepsis Six guidelines in emergency general surgery. *British Journal of Surgery*, *104*(2), e165-e171. https://doi.org/10.1002/bjs.10432

Multicentre observational study of adherence to Sepsis Six guidelines in emergency general surgery

UK National Surgical Research Collaborative*

*Members of the UK National Surgical Research Collaborative are co-authors of this study and can be found under the heading Collaborators

Correspondence to: Dr S. Strong, Centre for Surgical Research, University of Bristol, School of Social and Community Medicine, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK (e-mail: natalie.blencowe@bristol.ac.uk)

Background: Evidence-based interventions may reduce mortality in surgical patients. This study documented the prevalence of sepsis, adherence to guidelines in its management, and timing of source control in general surgical patients presenting as an emergency.

Methods: Patients aged 16 years or more presenting with emergency general surgery problems were identified over a 7-day period and then screened for sepsis compliance (using the Sepsis Six standards, devised for severe sepsis) and the timing of source control (whether radiological or surgical). Exploratory analyses examined associations between the mode (emergency department or general practitioner) and time of admission, adherence to the sepsis guidelines, and outcomes (complications or death within 30 days).

Results: Of a total of 5067 patients from 97 hospitals across the UK, 911 (18.0 per cent) fulfilled the criteria for sepsis, 165 (3.3 per cent) for severe sepsis and 24 (0.5 per cent) for septic shock. Timely delivery of all Sepsis Six guidelines for patients with severe sepsis was achieved in four patients. For patients with severe sepsis, 17.6–94.5 per cent of individual guidelines within the Sepsis Six were delivered. Oxygen was the criterion most likely to be missed, followed by blood cultures in all sepsis severity categories. Surgery for source control occurred a median of 19.8 (i.q.r. 10.0–35.4) h after diagnosis. Omission of Sepsis Six parameters did not appear to be associated with an increase in morbidity or mortality.

Conclusion: Although sepsis was common in general surgical patients presenting as an emergency, adherence to severe sepsis guidelines were incomplete in the majority. Despite this, no evidence of harm was apparent.

+A: Introduction

General surgical patients presenting as an emergency account for over 7 per cent of hospital episodes in the USA and 14 000 ICU admissions per year in the UK[1–3]. Sepsis is prevalent in this patient group. Early diagnosis of severe sepsis and initiation of goal-directed therapy can reduce mortality, irrespective of the need for surgery[4,5]. This evidence was used to develop a care bundle known as the Sepsis Six for managing patients with severe sepsis (*Table 1*)[6,7]. These standards have been endorsed by many professional organizations, including the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the Royal Colleges of Surgeons of England and Ireland[1,2,8,9]. Complete application of these interventions is thought to be associated with as much as a one-third reduction in mortality from sepsis, although uptake is uncertain amongst surgical patients presenting as an emergency[4,6].

The main aims of the present study were to assess adherence to the Sepsis Six guidelines and identify the timing of source control in general surgical patients presenting with an emergency condition. A secondary aim was to explore associations between adherence to the guidelines and complications or death.

+A: Methods

This study was conducted according to a prespecified protocol that was tested initially in three hospitals for feasibility. Each participating centre registered the project with their local audit and research department before commencement.

+B: Centre eligibility

Hospitals providing acute general surgical services were eligible to participate. Eligible centres were identified through networks of surgical trainee research collaboratives[10].

+B: Patient eligibility

Patients aged 16 years and over, presenting as unplanned admissions to the general surgical department, were eligible for inclusion. For the purposes of this study, the term general surgery encompassed patients with gastrointestinal, vascular or breast conditions. Emergencies from urology, neurosurgery, plastics, obstetrics and gynaecology, ear nose and throat, cardiothoracic, ophthalmology and maxillofacial surgery were excluded. In cases of diagnostic uncertainty (such as abdominal pain with a potential urological or gynaecological origin), patients were included if they were managed under the care of a general surgeon during the first 24 h of their admission. Patients presenting to paediatric surgical departments and inpatient referrals from other medical specialties were excluded.

+B: Identification of eligible patients

Over a predefined 7-day interval from 21 to 28 October 2013, patients were identified at each participating hospital by interrogating electronic or hand-written records depending on local hospital policy. Patients' unique identification numbers were entered into a database and stored securely at each hospital until data extraction was undertaken.

+B: Data collection

Data were collected for a total of 30 days after admission to hospital. Methods used to retrieve relevant information varied between hospitals, but was typically by interrogation of patients' medical records performed by teams of surgical trainees within each hospital. Demographic data were recorded, including sex, age, method of referral and time of admission. The presence or absence of sepsis was elicited, as defined below, for the first 24 h of each patient's hospital admission. Time of admission was taken as the time each patient was first seen by a hospital doctor (either via the emergency department (ED) or as a general practitioner (GP) referral).

To fulfil the diagnostic criteria for sepsis (systemic inflammatory response syndrome plus clinical suspicion or confirmation of an infective source; *Appendix S1*, supporting information), contemporaneous evidence of at least two parameter abnormalities (physiological or laboratory markers) was required. Physiological signs of sepsis had to be present simultaneously, whereas abnormal laboratory parameters needed to occur within 12 h (white cell count) or 1 h (glucose) of physiological signs. An online exercise (containing detailed scenarios) was developed by the study team and completed by local investigators to ensure a unified approach to diagnostic criteria.

If patients did not meet the diagnostic criteria for sepsis, no further data collection was performed. In patients meeting the criteria, the severity of sepsis was categorized (according to international consensus definitions[11]) and adherence to the Sepsis Six guidelines (*Table 1*) was assessed. Although the Sepsis Six guidelines were originally developed to treat patients with severe sepsis or septic shock, this study assessed compliance amongst all patients with sepsis, due to anticipated difficulties with categorizing sepsis severity.

Complications (according to standard criteria[12]; *Appendix S2*, supporting information), 30-day mortality, length of hospital stay, length of ICU stay and hospital readmission rates were recorded for 30 days after admission.

+B: Data management and analysis

Information was entered into a password-protected online database in each of the participating hospitals. Data on compliance with the Sepsis Six guidelines were summarized with descriptive statistics. Multivariable regression modelling was used to test for associations between: route (GP or ED) and time of admission, and non-compliance with the recommendations; and non-compliance with any or all of the components of the Sepsis Six parameters, and complications or death. Multivariable regression was also used to analyse patterns of missing data,

compliance with the Sepsis Six guidelines with sex, time or route of admission, age, or severity of sepsis. Stata® version 14 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

+A: Results

+B: Demographics

A total of 5067 patients (56.0 per cent female) from 97 centres were included (*Table 2*). The majority were referred to surgical teams from the ED (3014, 58.6 per cent). Amongst the 5067 patients, 911 (18.0 per cent) fulfilled the criteria for sepsis, 165 (3.3 per cent) for severe sepsis and 24 (0.5 per cent) for septic shock. Overall, ten of the 24 patients (42 per cent) with septic shock were either discussed with intensivists or transferred to the ICU. The most common diagnoses were biliary disease and appendicitis (*Table 3*).

+B: Adherence to the Sepsis Six guidelines

Delivery of all Sepsis Six guidelines was achieved in 4.8 per cent of the patients (*Table 4*). Highest compliance was seen for the measurement of full blood count (93.2 per cent) and delivery of antibiotics (76.3 per cent), although blood cultures were seldom collected (26.0 per cent). Neither the source (ED or GP) nor time of referral (day, evening or night) influenced compliance with the Sepsis Six guidelines.

+B: Source control and discussion with ICU staff

Of patients fulfilling the diagnostic criteria for sepsis, 37.1 per cent underwent surgical intervention for source control (*Table 5*). The most commonly performed surgical procedure was appendicectomy. The median time to source control ranged from 18.5 to 24.6 h.

+B: Outcomes

The mean duration of hospital stay for patients with sepsis was 4 days (*Table 6*). Death in hospital (within 30 days) occurred in 39 (4.3 per cent) of patients with sepsis. No association was found between the development of complications or death and omission of any of the Sepsis Six components. Risk factors for mortality included oxygen delivery (β coefficient 0.10, 95 per cent c.i. 0.05 to 0.15), arterial blood gas sampling (0.04, 0.00 to 0.08) and receiving all of the Sepsis Six interventions (0.12, 0.06 to 0.18), all of which reflect the likely need for ICU admission.

+A: Discussion

Sepsis is prevalent in surgical patients[13]. A recent analysis of the American College of Surgeons National Surgical Quality Improvement Project database found that sepsis and septic shock are ten times more common than perioperative myocardial infarction or pulmonary embolism in the general surgery population[14]. However, accurate identification of sepsis and early source control presents particular challenges amongst surgical patients, because they may require advanced imaging and complex operative interventions for diagnosis to be confirmed. Treatment strategies aim to identify at-risk patients early to prevent progression to severe sepsis, septic shock or death. In this study, most patients with severe sepsis or septic shock received some but not all of the Sepsis Six interventions, but this did not influence mortality. Others have examined the effect of performance improvement programmes on compliance with sepsis care bundles in both emergency department and ICU settings. Baseline compliance was poor (11–19 per cent), and increased modestly (up to 31 per cent) following improvement programmes[15,16].

The delays evident in the present study may represent clinical uncertainty, a failure to identify septic patients early, or a lack of knowledge regarding the required interventions once the diagnosis of sepsis had been made[17,18]. It is important to note that omission of the

Sepsis Six did not alter outcomes in this study. This may be because the Sepsis Six guidelines could be excessive for many surgical patients, for example those with uncomplicated perianal abscesses, cholecystitis or appendicitis in whom timely operative intervention is planned. A second reason is that the approach to sepsis amongst surgical patients often requires interventional treatment (such as drainage or organ removal) compared with the non-interventional treatment of patients with non-surgical diagnoses (for example, urinary or respiratory tract infections). As such, surgeons may focus primarily on delivering the surgical intervention rather than the Sepsis Six components. In this study, source control was not achieved within the time limits recommended by the Royal College of Surgeons of England[1] (18 h for sepsis, 6 h or less for severe sepsis, and immediate surgery for septic shock). Although reasons for delay were not specifically examined, previous studies[19,20] have suggested these to be multifactorial, largely reflecting administrative, capacity and staffing issues.

The timely administration of antibiotics is particularly important[21–23]. The mortality rate from severe sepsis approaches 35 per cent, and several studies[21,23] have demonstrated a survival benefit for patients treated with empirical antibiotics within 1 h of diagnosis Although three-quarters of patients were given antibiotics, only one-third were delivered within 1 h of diagnosis. However, it may not always be necessary to deliver antibiotics within this time frame, for example in 'well' patients in whom timely operative intervention is planned. Moreover, antibiotics are a direct cause of significant health problems such as allergic reaction, *Clostridium difficile* infection and the development of resistance. It is therefore paramount that clinicians carefully balance antibiotic prescription against the potential risks; this includes ensuring that their use is limited to patients in whom antimicrobial therapy is absolutely necessary. Further consideration of the appropriateness of the Sepsis Six guidelines in surgical patients is therefore required. A risk stratification tool

would enable the use of opt-out parameters to avoid overtreatment, as well as timely recognition of unwell patients requiring urgent Sepsis Six delivery before operative intervention.

There are several limitations that must be considered when interpreting the results. In designing this study, the authors were keen to ensure that patients were identified prospectively. In doing so, however, they were concerned that participation may alter usual behaviour. To address this, trainees were asked to maintain a list of all patients presenting to the emergency general surgery team during the 7 days of data collection. They were asked to wait 30 days before collecting data regarding sepsis. Missing data were also a problem, particularly the timing of Sepsis Six administration. To examine the patterns of missing data regarding the administration of the Sepsis Six interventions, multivariable regression was performed. This showed that patients with missing data were more likely to have been admitted from the ED and to have sepsis rather than severe sepsis or septic shock. It would have been of interest to compare the mortality rates of patients with and without sepsis, preferably by recording 90-day instead of 30-day mortality. The authors were concerned, however, that recording data over a longer time period might have resulted in loss of engagement with the many trainees participating in this study. Finally, although trainees completed an online learning package to assess their ability to diagnose and categorize sepsis, this did not necessarily guarantee that data extraction was accurate.

The importance of the appropriate treatment of sepsis has recently been acknowledged by NHS England and has been adopted for the Commissioning for Quality and Innovation (CQUIN) payment framework[24]. This will link the screening and timely treatment of patients with sepsis with a proportion of provider income, and has already resulted in a number of initiatives to optimize outcomes for sepsis, such as the development diagnostic and risk stratification toolkits. This study has highlighted that the Sepsis Six guidelines did not

improve outcomes for surgical patients presenting as an emergency. Development of a risk stratification tool would represent an important step to target those who might benefit most while avoiding overtreatment in the current era of antibiotic resistance.

+A: Core study group

Blencowe N, (Centre for Surgical Research, University of Bristol, Bristol, UK)

Strong S (Centre for Surgical Research, University of Bristol, Bristol, UK)

Blazeby J (Centre for Surgical Research, University of Bristol, Bristol, UK)

Daniels R (UK Sepsis Trust)

Peden C (Department of Anesthesiology, Keck School of Medicine, University of Southern California, USA)

Lim J (University Hospitals Bristol, NHS Foundation Trust)

Messenger D (University Hospitals Bristol, NHS Foundation Trust)

Richards S (Royal United Hospital, Bath, UK

Rogers C (Clinical Trials and Evaluation Unit, Bristol, UK)

Trickey A (University of Bristol, UK)

Carpenter C (North Bristol NHS Trust, UK)

Stark H (University Hospitals Bristol, NHS Foundation Trust)

This study was conceptualized by N.S.B., S.S, S.R, C.P. and R.D.. Data collection was coordinated by N.S.B., S.S., J.L., C.C. and H.S. J.L. designed the study database and was assisted by N.B and S.S..Data analysis was performed by N.S.B., A.T., S.S. and C.R.. N.S.B. and S.S. wrote the first draft of the manuscript, which was edited by all members of the core study group. N.S.B and S.S. are the guarantors for this paper.

+A: The following trainee members of the National Surgical Research Collaborative collected data

Fadhlillah M, Jai W (Addenbrooke's Hospital, UK)

Balakumar R, McHugh R, Proctor V, Wild J (Barnsley Hospital, UK)

Aldugman S, Atwell A, Buchan L, Castellimo N, Craig N, Dindyal S, Hansell F, Haque A, Magee S, Manson J, Menon J, Tuckmacjy H (Basildon University Hospital, UK)

McDermott F (Beaumont Hospital, UK)

Lotfi N, Sarmah P (Birmingham Heartlands Hospital, UK)

Allen N, Heywood N, Rees A (Blackpool Victoria Hospital, UK)

Brigic A (Bradford Royal Infirmary, UK)

Ali A, Brown J, Gupta S, Hui D, Lewis R, (Carmarthen General Hospital, UK)

Bagenal J, Dua A, Khatri C, Park C (Chelsea and Westminster Hospital, UK)

Bennett J, Brennan A, Pearce O, Shah R, Twelves D, Woods S. (Cheltenham General Hospital, UK)

Jarvis A, White A (Chesterfield Royal Hospital, UK)

Blower E, Veitch J (Countess of Chester Hospital, UK)

Nicholson G (Crosshouse Hospital, UK)

Chatzikonstantinou M, Wheatstone S (Darent Valley Hospital, UK)

Shaban F (Darlington Memorial Hospital, UK)

Bartlett A, Kimble A, Glazier J, Jones M, Pengelli S (Derriford Hospital, Plymouth Hospital NHS trust, UK)

Al-Jundi W, El Sharif M, Frizzini C, Wilson T (Doncaster Royal Infirmary, UK)

; Ashman A, Fallaize R, Hallam S, Simmons L (North Bristol NHS Trust, UK)

Frank L, Griggs R, Hardy T, Lyn-White N, Mason M (Gloucestershire Hospital NHS foundation trust, UK)

Carnaby G, Jhah J, Stuttaford L, Upchurch E (Great Western Hospital, NHS foundation trust, UK)

Cunha P, Kaptanis S, Tayeh S, Shamsul M (Homerton University Hospital, UK)

Games K, Iftikhar H, Parthasarathy M (Ipswich Hospital, UK)

Bonastos V, Taffaha, H (James Paget University Hospital, UK)

Bew D, Ng J, Liasis L (Kings College Hospital, UK)

Gerçek Y, Moos B, Reilly J (Kings Mill Hospital, UK)

Hicks G (Leeds General infirmary, UK)

Chawla A, Miller A, Satheesan K (Leicester Royal Infirmary, UK)

Duncan A, Vlachogiorgis A (Lister Hospital, UK)

Sengupta N (Luton and Dunstable University Hospital, UK)

Mowbray N (Morristan Hospital, UK)

Barrow E, Smith S (Manchester Royal Infirmary, UK)

Fudulu D, Hanks K, Jones A, McNair A, Oliphant Z, Weaver H(Musgrove park Hospital, UK)

Ranga N (New Cross Hospital, Wolverhampton, UK)

Chisti T, Imatitikua T, Jones T, Khan A, Ogunrinde I (Newham University Hospital, UK)

; Mittapalli D, Powell-Bowns M, Samuel M, Wilson M (Ninewells Hospital, UK)

; Bilki D, Nepdodiev D, Panagiotopoulou Y (Norfolk and Norwich Hospital, UK)

Halkias C (North Middlesex Hospital, UK)

Cattle K, Challand C (Peterborough City Hospital, UK)

Bandari S, Chambers A, Nguyen J, Walker K, Zamurrad M (Pilgrim Hospital Boston, UK)

Asarbakhsh M, Cracium M, (Pinderfield Hospital, UK)

Fatine Y, Khan S (Princess Alexandra Hospital, UK)

Lort S, Futaba K (Queen Elizabeth Hospital, Birmingham, UK)

Ban V, Cheng J, Kambasha C, Rizki H, Somaratne K, Wilson A (Queen Elizabeth Hospital, King's Lynn, UK)

Al Omran Y, Anwuzia-iwegbu C, Yakandawala G (Queens Hospital, Romford, UK)

; Richards C, Warner B (Raigmore Hospital, UK)

; Graffy H, MacInnes E, Nicholas J, Zakerhi R, (Rotherham Hospital, UK)

; Barrow P, Doran J, Ewan L (Royal Blackburn Hospital, UK)

Hancock L, Law J (Royal Bolton Hospital, UK)

Brewer H, Henderson I, Palser T, Murphy J, Nduwayo S, Saggu G (Royal Derby Hospita, UK l)

Brown C, Brown E, Dyke K, Evans T, Jenkins M, Lowe J (Royal Glamorgan Hospital, UK)

Brown C, Preet R (Royal Gwent Hospital, UK)

O'Reilly D, Symons N, Torrance H (Royal London Hospital, UK)

Corbett D, Kelly M, Khan T, Ali M, Poon S (Royal Liverpool University Hospital, UK)

Charleston P, Gill M, Martin J, Overton J, Sekhar H, (Royal Oldham Hospital, UK)

Adam U, Almari F, Basson R, Denny N, Khaw R, Goatman C, Slawinski C (Royal Preston Hospital, UK)

Evans R (Royal Shrewsbury Hospital NHS trust, UK)

Davies O, Halls M,Hotton E, Markham R, Potter S (Royal United Hospital Bath)

Foster M, Peristakeris I, Shaw S (Salford Royal NHS foundation trust, UK)

Marsden M (Salisbury District Hospital, UK)

Alshakarch J (Sandwell General Hospital, UK)

Ritchie J (Sheffield Teaching Hospital, UK)

Bajalan M, Choh C (Southampton General Hospital, UK)

Ahmed H, Khan F, Yasin S, Zafar A (Southend University Hospital, UK)

Oderuth E, Sheel A, Yuen-Chang F (Southport and Formby District General Hospital, UK)

Capozzi P (Stepping Hill Hospital, UK)

McGlone E, Loh Y (St George's University Hospitals NHS Trust, UK)

Cheong Soon W, Merrifield C, Scott A (St Mary's Hospital, UK)

El Kafsi J, Warner N (Stoke Madeville Hospital, UK)

Mohan H (St Vincent's University Hospital, UK)

Thomson P, Renshaw S, Walker D (University College Hospital NHS foundation trust, UK)

Carpenter C, Browning D, Burdall O, Butcher K, Greenwood A, Harris E, Merker L, Pegna V, Stark H. (University Hospitals Bristol NHS Foundation Trust, UK)

El-Sayed C, Gaunt A (University Hospitals Coventry NHS trust, UK)

Capozzi P, Newton K, Nicholson J, Pearce L. (University Hospital of South Manchester, UK)

Brown C, Brown C, Brown J, Jones A, Satherley L (University Hospitals of Wale, UK s)

Evans A, Lazarova L, Mcavoy A (Warrington Hospital NHS foundation trust, UK)

Spreadborough P (Warwick Hospital, UK)

Amin A, Bretherton C, Chapman A, Fleet M (Watford General Hospital) , UK

Challand C (West Suffolk NHS foundation trust, UK)

Jawad Z (West Midllesex University Hospital, UK)

Al-Hallao S, Botha E, Garcia P, Honeyman C. (Weston General Hospital, Weston are health NHS trust)

Byrne C (Wexford General Hospital)

Kabir I, Nana G (Wexham park Hospital)

English W (Whipps Cross University Hospital)

Broome J, Gilmore L, Goldsmith P, Krishnamohan N, Matsumoto K, Ren K, Rengifo C (Wigan Infirmary, UK)

West H (Wishaw Hospital)

Ellison A, Lloyd E, Stewart D, Stimpson A (Wrexham Maelor Hospital, UK)

Jones A (Yeovil District NHS foundation trust, UK)

Taylor G (York Teaching Hospital, UK)

Clutton J, Mortimer M, Mulla M (Ysbyty Gwynedd (Bangor) Hospital, UK)

Downey A (Belfast City Hospital, Northern Ireland)

Houston M (Mater Hospital, Northern Ireland)

Rapson K (Auckland City Hospital, New Zealand)

Davis N, Humphreys L (North Shore Hospital, New Zealand)

Barnard J (Middlemore Hospital, New Zealand)

Egbeare D, Whitlaw M (Royal Adelaide Hospital, Australia)

Zakirova R, (Toronto General Hospital, Canada**)**

+A: Acknowledgements

N.B. and S.S. contributed equally to this publication.

Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Definitions of sepsis (Word document)

Appendix S2 Definitions of complications (Word document)

Table 1 Sepsis Six guidelines

All of the following interventions should be performed within 1 h of diagnosis of severe sepsis:
Delivery of high-flow oxygen (15 l/min, in accordance with British Thoracic Society guidelines for critical illness, which includes sepsis)
Taking of blood cultures before administration of antibiotics
Administration of empirical broad-spectrum antibiotics
Administration of sufficient fluid resuscitation – give fluid challenges in divided boluses of 500 ml/h to a total volume of 30 ml/kg
Measurement of serum lactate concentration and full blood count
Commence accurate measurement of urine output (may require catheterization)

Table 2 Patient demographics

	No. of patients (*n* = 5067)	No. of patients with sepsis (*n* = 911)
Age (years)		
16–25	642 (12.8)	123 (13.6)
26–35	748 (15.0)	112 (12.4)
36–45	653 (13.1)	101 (11.2)
46–55	722 (14.4)	129 (14.3)
56–65	605 (12.1)	116 (12.8)
66–75	732 (14.4)	149 (16.5)
> 75	900 (18.0)	175 (19.3)
Missing	65	6
Sex		
M	2228 (44.0)	414 (45.5)
F	2836 (56.0)	496 (54.5)
Missing	3	1
Method of referral		
Emergency department	3014 (60.2)	593 (65.1)
General practitioner	1947 (38.9)	308 (33.8)
Other*	43 (0.9)	10 (1.1)
Missing	63	0
Time of admission		
08.01–18.00 hours	2584 (51.7)	431 (47.7)
18.01–00.00 hours	1447 (28.9)	274 (30.3)
00.01–08.00 hours	968 (19.4)	199 (22.0)
Missing	68	7
SIRS		
Yes	1709 (33.7)	911 (100)
No	3355 (66.3)	0 (0)
Missing	3	0
Category of sepsis		
Sepsis	911 (18.0)	911 (100)
Severe sepsis	165 (3.3)	165 (18.1)
Septic shock	24 (0.5)	24 (2.6)

Values in parentheses are percentages. *Direct referral from consultant surgeon, or self-referral to surgical assessment unit. SIRS, systemic inflammatory response syndrome.

Table 3 Diagnoses for patients with sepsis, severe sepsis or septic shock

Diagnosis*	Sepsis (*n* = 911)	Severe sepsis (*n* = 165)	Septic shock (*n* = 24)
Biliary disease	242 (26.6)	44 (26.7)	11 (46)
Appendicitis	164 (18.0)	28 (17.0)	0 (0)
Diverticulitis	89 (9.8)	11 (6.7)	1 (4)
Abscess	81 (8.9)	10 (6.1)	0 (0)
Urinary sepsis	52 (5.7)	11 (6.7)	0 (0)
Colitis or proctitis	35 (3.8)	7 (4.2)	0 (0)
Postoperative collection	18 (2.0)	2 (1.2)	1 (4)
Abdominal wall hernia	13 (1.4)	3 (1.8)	0 (0)
Wound infection	12 (1.3)	2 (1.2)	0 (0)
Peptic ulcer disease	11 (1.2)	4 (2.4)	1 (4)
Limb ischaemia	9 (1.0)	0 (0)	0 (0)
Inflammatory bowel disease	8 (0.9)	4 (2.4)	1 (4)
Tubo-ovarian pathology	6 (0.7)	0 (0)	0 (0)
Respiratory tract infection	5 (0.5)	1 (0.6)	0 (0)
Other	127 (13.9)	27 (16.4)	8 (33)

Values in parentheses are percentages. *Data missing for 20 patients.

Table 4 Adherence to the Sepsis Six guidelines

	Sepsis (*n* = 911)		Severe sepsis (*n* = 165)		Septic shock (*n* = 24)	
	Delivered at any time	Delivered in ≤ 1 h*	Delivered at any time	Delivered in ≤ 1 h*	Delivered at any time	Delivered in ≤ 1 h*
Delivery of high-flow oxygen	137 (15.0)	60 of 107 (56.1)	29 (17.6)	11 of 21 (52)	6 (25)	4 of 5 (80)
Missing	98	28	12	8	2	1
Blood cultures obtained before antibiotic administration	237 (26.0)	158 of 179 (88.3)	46 (27.9)	29 of 34 (85)	8 (33)	7 of 7 (100)
Missing	92	57	9	12	3	1
Administration of empirical broad-spectrum antibiotics	695 (76.3)	145 of 468 (31.0)	126 (76.4)	32 of 80 (40)	19 (79)	7 of 15 (47)
Missing	55	197	6	46	2	4
Initial fluid resuscitation	447 (49.1)	147 of 272 (54.0)	97 (58.8)	32 of 55 (58)	15 (63)	8 of 12 (67)
Missing	85	175	15	42	1	3
Measurement of serum lactate†	322 (35.3)	167 of 233 (71.7)	84 (50.9)	42 of 61 (69)	18 (75)	11 of 16 (69)
Missing	135	89	10	23	1	2
Measurement of FBC†	849 (93.2)	418 of 537 (77.8)	156 (94.5)	69 of 87 (79)	23 (96)	14 of 18 (78)
Missing	47	312	6	69	1	5
Urine output measured at least every 4 h	330 (36.2)	54 of 121 (44.6)	79 (47.9)	14 of 30 (47)	16 (67)	3 of 12 (25)
Missing	176	209	17	49	3	4
All Sepsis Six components adhered to	44 (4.8)	12 of 633 (1.9)	13 (7.9)	4 of 111 (3.6)	4 (17)	0 (0)

Values in parentheses are percentages; *the percentage delivered within 1 h, excluding patients where timings were not recorded. †Serum lactate and full blood count (FBC) comprise a single intervention in the Sepsis Six guidelines, but were recorded separately for the purposes of this study.

Table 5 Source control

	Sepsis (*n* = 911)	Severe sepsis (*n* = 165)	Septic shock (*n* = 24)
Time to source control (h)*	19.8 (10.0–35.4)	18.5 (6.8–25.9)	24.6 (8.7–24.9)
Surgical intervention	338 (37.1)	62 (37.6)	9 (38)
Appendicectomy	125	25	0
Abscess drainage	83	13	1
Laparoscopy/laparotomy†	42	8	1
Cholecystectomy	26	1	1
Large bowel resection	16	4	2
Small bowel resection	12	3	2
Hernia repair	8	2	0
Wound debridement	5	0	0
Amputation	3	0	0
Adhesiolysis	2	0	0
Unknown	14	6	2
Other	2	0	0
Radiological intervention	7 (0.8)	3 (1.8)	0 (0)
Endoscopic intervention	12 (1.3)	1 (0.6)	0 (0)

*Values are median (i.q.r.). †With no bowel resection.

Table 6 Outcomes according to category of sepsis

	No. of patients*		
	Sepsis (*n* = 911)	Severe sepsis (*n* = 165)	Septic shock (*n* = 24)
Duration of hospital stay (days)*	4 (2–8)	5 (3–8)	9.5 (6–25)
In-hospital death within 30 days	39 (4.3)	8 (4.8	6 (25)
Complication	120 (13.2)	27 (16.4)	9 (38)
Duration of ICU stay (days)*	0 (0–1)	0 (0–0)	5 (3–6)
Readmission to hospital within 30 days	86 (9.4)	10 (6.1)	1 (4)

*With percentages in parentheses unless indicated otherwise; *values are median (i.q.r.).