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The microbiology and outcome of sepsis in Victoria, Australia

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SUMMARY

We analysed data from 33 741 patients with ICD-10-AM-defined sepsis from an Australian hospital morbidity dataset to investigate the relationships between specific types of organisms, potential risk factors for infection, organ dysfunction, ICU utilization and hospital mortality. A total of 24% of patients received some of their care in an intensive care unit, and the overall hospital mortality rate was 18%. Gram-positive bacteria were isolated in 27% of cases and Gram-negative bacteria in 20%. Sepsis due to *Staphylococcus aureus* was associated with vascular and joint devices whereas *Pseudomonas aeruginosa* and Gram-negative rods were more common with genitourinary devices and lymphoproliferative disease. Sepsis-associated organ dysfunction most commonly involved the respiratory system, followed by the renal and circulatory systems. These patterns may provide useful clues to the pathogenesis and therapy of this often fatal syndrome which is a major ongoing problem for hospitalized patients.

INTRODUCTION

Serious infection and its resultant clinical syndromes termed severe sepsis and septic shock account in North America for as many adult deaths annually as myocardial infarction, with the incidence of these disorders projected to increase by 1·5% per annum [1]. This high mortality is confirmed by recent international data in which the 28-day mortality for adult patients with sepsis ranged from 30·8 to 49·2% [2–5]. Moreover, the intensive care unit (ICU) mortality for adults with septic shock, the most severe of the clinical sepsis states, has been reported to be as high as 60·1% [3]. In addition, critical care support of a single patient with sepsis may generate more than US$29 000 in direct hospital costs per admission [1]. Increased knowledge about the specific microbiological causes of sepsis may be crucial in improving the high morbidity and mortality of the disease.

Microbiological patterns in sepsis have changed considerably over the last 20 years, with a shift from Gram-negative to Gram-positive bacterial sepsis as the most frequent causative organism [4]. This shift may be a contributing factor to the persistently high mortality in septic shock, perhaps confounding continuous incremental improvements in intensive care practices and the expanding spectrum of available antibiotics.

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Previous studies have dealt with microbial factors with respect to specific microorganisms within a localized, often academic, hospital setting rather than broadly in time and place [2, 5]. Our aim was to investigate the relationships between specific types of organisms, predisposing factors and outcomes in a large population of septic patients identified in an Australian state-based hospital morbidity dataset.

MATERIALS AND METHODS

Data source

Victoria is Australia's second largest state with a population over 4·5 million [6]. As part of the universal Australian health system, each state's health authority collects administrative data on all hospital admissions and ensures data standards through routine external audit. The Victorian Admitted Episodes Dataset (VAED), maintained by the Victorian State Department of Human Services, is based on hospital data collected by individual private and public hospitals in the state of Victoria [7]. This dataset contains demographic and clinical information on each episode of patient care, with the clinical information coded using the ICD-10-AM format [8].

Period of analysis and case definitions

The analysis period was for 4 years from 1 July 1999 to 30 June 2003 during which time there were 3 122 515 overnight admissions, all of which were included in our analysis.

The presence of sepsis during a hospitalization was defined using the ICD-10-AM codes for Gram-positive (due to staphylococci or streptococci), Gram-negative, fungal, tuberculous, and anaerobic organisms and for microbiologically undefined sepsis in any of the diagnostic codes. Specimens from sterile sites were collected and processed using standard individual hospital protocols. The Australian coding standards of sepsis are explicit utilizing The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis [9]. In 1999/2000 for each discharge only a maximum of 12 diagnostic codes were recorded whereas up to 25 were recorded for the remaining 3 years.

Potential risk factors including immune dysfunction, diabetes, intravascular devices and prosthetic joint devices were defined using their ICD-10-AM codes. The selection of these risk factors was based on the consensus of two physicians (V.S. and K.V.) and assessed for face validity by a third (T.K.).

Organ dysfunction resulting from sepsis

Organ dysfunction was defined by translating the ICD-9 codes used by Martin and others [4] to ICD-10-AM codes and when present at any time during the hospitalization were considered to be a complication of the episode of sepsis.

Data analysis

The goal of the analysis was to describe: (1) the spectrum of causative organisms in sepsis; (2) associations between these organisms and defined risk factors; and (3) the impact of specific organisms on pertinent outcomes, such as organ dysfunction, in-hospital mortality, and health service utilization.

The results were generally presented as proportions and the following statistical tests were used to assess the significance of the associations:

To identify the statistical significance of an association between a risk factor and a causative organism, separate logistic regression models were fitted for each organism. The reference group was the 'no risk factor' group. These were bivariate models only; no adjustment for age, gender or other covariates was made in order to provide a descriptive microbiological risk profile to guide initial treatment. Only strong associations were highlighted, that is, associations between a risk factor and organism with a point estimate for the odds ratio (OR) of $\geqslant 2$ whose 95% confidence interval (CI) did not include 1.

To assess the relationship of an organism with pertinent outcomes including requirement of ICU care, organ dysfunction and in-hospital death, separate bivariate logistic regression models were fitted for each outcome. Again only strong associations were considered highlighted. The reference group for these analyses was the causative organism *Escherichia coli*, as this species was associated with the most favourable outcomes.

The median and 25th–75th percentile of length of stay for both ICU and in-hospital were determined overall and for each organism. All data extraction and analysis were conducted using SAS 8.2 [10]. Permission to analyse and publish these (de-identified) data was provided by the Victorian Department of Human Services.

Table 1. *Characteristics of patients with sepsis*

	n	%
Total	33 741	100·0
Year		
1999–2000	7342	21·8
2000–2001	8149	24·2
2001–2002	8824	26·1
2002–2003	9426	27·9
Age (years)		
<1	2683	8·0
1–9	467	1·4
10–19	570	1·7
20–29	1208	3·6
30–39	1665	4·9
40–49	2337	6·9
50–59	3611	10·7
60–69	5378	15·9
70–79	8538	25·3
80–89	6084	18·0
⩾90	1200	3·6
Gender		
Female	15 065	44·6
Male	18 676	55·4
Admission status*		
Elective	9654	28·6
Emergency	23 372	69·3
Unspecified	715	2·1
Type of hospital†		
Teaching	20 393	60·4
Private	6005	17·8
Other	7131	21·1
Unspecified	212	0·6

* Elective admissions are planned admissions whereas emergency admissions are unplanned.
† Teaching and other hospitals are publicly funded hospitals.

Table 2. *Frequency of risk factors for sepsis*

	Total (*n* = 33 741)	%
Type of risk factor		
No risk factor	15 643	46·4
Non insulin dependent diabetes mellitus	3486	10·3
Chronic renal failure	2742	8·1
Neutropenia	2526	7·5
Lymphoproliferative	1883	5·6
Vascular or joint device	1355	4·0
Following procedure	1330	3·9
Metastatic cancer	1300	3·9
Solid tumour, no metastases	934	2·8
Autoimmune disease	636	1·9
Transplant	455	1·4
Chronic hepatic failure	434	1·3
Insulin dependent diabetes mellitus	375	1·1
Peritoneal dialysis catheter	253	0·8
Inherited immune deficiency	148	0·4
Genitourinary device	147	0·4
Asplenia	63	0·2
HIV	31	0·1
Number of risk factors		
0	15 643	46·4
1	10 101	29·9
2	5908	17·5
3	1781	5·3
4	275	0·8
5	32	0·1
6	1	0·0

RESULTS

General study characteristics

During the 4-year study period there were 33 741 recorded cases of sepsis among the 3 122 515 hospitalized patients (Table 1). The incidence of sepsis increased with advancing age and showed a slight male preponderance. Most cases were treated in large teaching hospitals. No pre-specified risk factors were found in 46% of the patients, one risk factor was found in 30%, and two or more risk factors were found in 23% (Table 2).

A potentially causative organism was identified in 18 548 patients (55%) (Table 3). The organisms most commonly isolated were *Staphylococcus aureus* (13%), *E. coli* (11·5%), and Group A streptococci and other streptococci (8%). Only 3% of patients had ICD-10-AM codes for more than one organism. Overall Gram-positive cocci were identified in 28% of patients with sepsis and Gram-negative rods in 20%.

Resistance to antimicrobial therapy was evaluated for *S. aureus*. The rate of methicillin-resistant *S. aureus* (MRSA) was 27% (data not shown).

A total of 24% of admissions with sepsis received some of their in-patient treatment in an ICU (Table 4). Organ dysfunction most frequently involved the lungs, followed by the renal and circulatory systems. Multiple organ dysfunction involving two or more systems occurred in 17% of sepsis patients (Table 4). Death occurred in 18% of all sepsis patients.

Microbiology of sepsis in relation to risk factors

In comparison to those patients without any recorded risk factors (Table 5), *S. aureus* was identified more commonly in certain patients, especially those with vascular and joint devices (OR 5·1, 95% CI 4·7–5·7),

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Table 3. *Microbiology of sepsis*

	Total ($n=33\,741$)	%
Type of microorganism		
Unspecified organism	15 193	45·0
S. aureus	4532	13·4
E. coli	3885	11·5
Streptococci, other	2467	7·3
Gram-negative rods, other	2221	6·6
Coagulase-negative staphylococci	2151	6·4
Specified, other bacteria	1121	3·3
Pseudomonas	637	1·9
Legionella	477	1·4
Meningococcus	289	0·9
Candida/other fungi	284	0·8
Anaerobes	181	0·5
Streptococcus, Group A	180	0·5
M. tuberculosis	70	0·2
H. influenzae	53	0·2
Number of organisms		
0	15 193	45·0
1	17 675	52·4
2	793	2·4
3	69	0·2
4	10	0·0
5	1	0·0

Table 4. *Organ dysfunction, ICU care and in hospital mortality for septic patients*

	Total ($n=33\,741$)	%
Dysfunctional organ		
Respiratory	5568	16·5
Renal	5520	16·4
Cardiovascular	4979	14·8
Hepatic	124	0·4
Hematological	2581	7·6
Metabolic	1786	5·3
No. of dysfunction organs		
0–1	28 179	83·5
2 or more	5562	16·8
ICU stay during admission	8024	23·8
In-hospital death	6216	18·4

ICU, Intensive care unit.

following procedures (OR 3·1, 95% CI 2·8–3·5), with peritoneal dialysis catheters (OR 2·3, 95% CI 1·8–2·9) and in asplenia (OR 2·0, 95% CI 1·2–3·4). Sepsis due to *E. coli* was associated with chronic hepatic failure, diabetes and malignancy; however, the OR of all of these associations was <2. *Pseudomonas* and other Gram-negative rods were most common in patients with genitourinary devices (OR 2·6, 95% CI 1·8–3·8) and lymphoproliferative disease (OR 2·0, 95% CI 1·3–5·4). All species of streptococci were most commonly associated with HIV infection (OR 2·7, 95% CI 1·8–3·8). Peritoneal dialysis catheters (OR 3·3, 95% CI 2·5–4·3) or vascular/joint devices (OR 2·3, 95% CI 2·0–2·6) were most strongly associated with coagulase-negative staphylococcal sepsis. Fungal sepsis was increased in HIV infection (OR 17·0, 95% CI 7·2, 40·6), following procedures (OR 4·5, 95% CI 3·3–6·3), peritoneal dialysis catheters (OR 3·8, 95% CI 2·2–6·7), genitourinary devices (OR 3·5, 95% CI 1·5–8·2), vascular/joint devices (OR 3·5, 95% CI 2·6–4·7), autoimmune disease (OR 2·6, 95% CI 1·6–4·4) and lymphoproliferative disease (OR 2·1, 95% CI 1·5–3·0). The CI for the association between asplenia and *Candida* and other fungal infections included unity. No particular patterns were notable for other specified organisms or unspecified, clinically determined sepsis.

Microbiology of sepsis in relation to organ dysfunction

Candida sp. was associated with multiple organ dysfunction syndrome (OR 3·7, 95% CI 2·8–4·9), as was the isolation of *S. aureus* (OR 2·2, 95% CI 1·9–2·5), other staphylococcal species (OR 2·1, 95% CI 1·8–2·5) and sepsis where no organism was specified (OR 2·0, 95% CI 1·8–2·3) (Table 6).

Microbiology of sepsis in relation to outcome

Patients with sepsis due to *Candida* sp. and other fungi were more likely to be admitted to an ICU than patients with non-fungal sepsis and received a median of 8 days of ICU care (Table 7). Moreover, patients with fungal sepsis had a high mortality (OR in comparison to *E. coli* 3·8, 95% CI 2·8–5·0), followed by unspecified organisms (OR 3·7, 95% CI 3·2–4·1) and *S. aureus* (OR 2·5, 95% CI 2·2–2·9). Although coagulase-negative staphylococci had a higher median ICU length of stay compared to other identified organisms (14 days), their associated mortality was lower (12·8%). ICU usage was also markedly increased in those with *S. aureus* sepsis, with 31% of patients being admitted to an ICU (Table 8). Septic patients without an identified organism had a high mortality (24·9%).

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Table 5. *Microbiology of sepsis in relation to risk factors*

	Type of microorganism, % of all patients with sepsis ($n=33\,741$)							
	S. aureus	*E. coli*	*Pseudomonas*/ other GNR	Strepto-cocci*	Specified organisms†	Coagulase-negative staphylococci	*Candida*/ other fungi	Unspecified organisms
Overall frequency	13·4	11·5	8·5	7·8	6·5	6·4	0·8	45·0
Risk factor								
Nil	10·4	12·5	6·9	9·6	7·6	6·4	0·5	46·2
NIDDM	10·8	14·5	7·9	7·0	5·5	3·9	0·5	49·7
Chronic renal failure	12·8	13·0	7·6	6·5	5·6	4·4	0·6	49·5
Neutropenia	10·9	9·5	12·0	6·2	5·0	8·3	1·1	47·1
Lymphoproliferative	13·3	6·7	**13·5**	7·4	6·3	7·3	1·2	44·3
Vascular or joint device	**43·0**	3·1	9·5	5·1	5·4	**12·5**	**2·3**	19·1
Following procedure	**31·1**	8·2	10·1	4·7	4·4	6·7	**2·9**	32·0
Metastatic cancer	9·2	13·2	12·2	4·2	5·7	4·2	0·3	51·0
Solid tumour, no metastases	11·3	13·0	11·5	5·4	4·9	4·6	0·5	48·8
Autoimmune disease	20·1	8·3	9·4	6·4	5·3	6·8	**2·5**	41·1
Transplant	14·9	11·4	11·9	7·9	7·7	7·7	1·1	37·4
Chronic hepatic failure	13·4	14·5	6·9	9·2	4·4	3·7	0·5	47·5
IDDM	15·2	12·5	4·5	5·9	5·6	6·7	0·8	48·8
Peritoneal dialysis catheter	**20·9**	3·2	8·7	5·9	5·1	**21·3**	**4·7**	30·0
Inherited immune deficiency	19·6	5·4	6·1	11·5	10·1	3·4	0·7	43·2
Genitourinary device	15·6	12·9	**19·7**	3·4	6·1	6·1	**2·0**	34·0
Asplenia	**20·6**	1·6	4·8	9·5	9·5	6·3	3·2	44·4
HIV	16·1	6·5	16·1	**22·6**	9·7	3·2	**9·7**	16·1

GNR, Gram-negative rods; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Proportions in bold indicate that the risk factor had an odds ratio of $\geqslant 2$ in a logistic regression model: assessing the association of each risk factor with the particular type of organism.

* Streptococci includes Group A and other streptococci.

† Specified organisms include *Legionella*, meningococcus, anaerobes, *M. tuberculosis*, *Haemophilus* and other specified bacteria.

Table 6. *Microbiology of sepsis in relation to organ dysfunction*

	Type of organ dysfunction, % of all septic patients ($n=33\,741$)							
Type of microorganism	Respiratory	Cardio-vascular	Renal	Hepatic	Haematologic	Metabolic	Neurologic	Multi-organ
S. aureus	21·3	15·1	18·7	0·4	9·0	4·6	5·3	**19·3**
E. coli	7·1	10·5	13·3	0·3	6·9	3·2	3·5	10·0
Pseudomonas/other GNR	12·3	13·5	14·7	0·2	9·1	3·8	4·1	13·7
Streptococci	13·7	10·9	11·1	0·4	7·3	3·5	3·3	11·9
Specified organisms*	16·5	10·6	12·7	0·2	7·1	3·9	2·7	13·1
Coagulase-neg. staphylococci	30·2	16·1	13·1	0·4	7·0	4·9	3·8	**19·0**
Candida/other fungi	**38·0**	16·9	**22·5**	**0·7**	**16·2**	**11·6**	4·6	**29·2**
Unspecified organism	16·4	17·0	18·6	0·4	7·2	6·8	**5·4**	**18·5**

GNR, Gram-negative rod.

Proportions in bold indicate that the type of microorganism had an odds ratio of $\geqslant 2$ in a logistic regression model: assessing the association of each organism with each outcome.

* Specified organisms include *Legionella*, meningococcus, anaerobes, *M. tuberculosis*, *Haemophilus* and other specified bacteria.

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Table 7. *Outcome and ICU care related to microbiology*

	% of all septic patients ($n=33\,741$)	
Type of microorganism	ICU care	In-hospital death
S. aureus	**30·5**	**18·4**
E. coli	14·1	8·3
Pseudomonas/other GNR	20·9	15·0
Streptococci	20·3	10·5
Specified organisms*	24·0	10·0
Coagulase-negative staphylococci	**38·2**	12·8
Candida/other fungi	**47·9**	**25·4**
Unspecified organism	22·9	**24·9**

ICU, Intensive care unit; GNR, Gram-negative rod.
Proportions in bold indicate that the type of microorganism has an odds ratio of $\geqslant 2$ in a logistic regression model: assessing the association of each organism with each outcome.
* Specified organisms include *Legionella*, meningococcus, anaerobes, *M. tuberculosis*, *Haemophilus* and other specified bacteria.

Table 8. *Microbiology of sepsis and hospital utilization*

		Length of stay, days		ICU stay, days	
Type of microorganism	*n*	Median	25th to 75th percentile	Median	25th to 75th percentile
Overall	33 741	10	5–22	5	2–14
S. aureus	4532	20	9–38	7	2–19
E. coli	3885	8	5–16	3	1–9
Pseudomonas and other GNR	2869	11	6–22	4	1–14
Streptococci	2636	9	5–19	5	2–11
Specified organisms*	2190	10	6–21	5	1–17
Coagulase-negative staphylococcus	2152	17	8–37	14	5–34
Candida/other fungi	284	29	14–50	8	3–18
Unspecified organism	15 193	8	4–18	4	1–10

ICU, Intensive care unit; GNR, Gram-negative rod.
* Specified organisms include *Legionella*, meningococcus, anaerobes, *M. tuberculosis*, *Haemophilus* and other specified bacteria.

DISCUSSION

This is the first study to relate specific microbiological information contained in a large centralized state health database to clinically important attributes of hospital patients with sepsis, including the extent of their organ dysfunction, ICU utilization and outcome. Analysis of data derived from more than 3·1 million hospital admission episodes over a 4-year period identified 33 741 cases of sepsis, nearly one-quarter of which received at least some of their care in an ICU. In addition to provision of clues to the pathogenesis of sepsis and septic shock, knowledge of the likely distribution of Gram-positive and Gram-negative organisms in hospital patients with sepsis has immediate practical implications, since the extent of treatment benefits in severe sepsis may vary by organism type [11].

The overall pattern of organisms associated with sepsis has changed considerably over the last 20 years [12]. Gram-negative bacteria, particularly Enterobacteriaceae, previously were involved in over 40% of cases of sepsis [13]. As with other recent investigations our study has shown that Gram-positive bacteria are now playing a predominant role [14–16], with staphylococcal and streptococcal species together accounting for nearly 28% of cases of sepsis, whereas Gram-negative organisms accounted for only 20%.

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This trend, which may be associated with an increased number of invasive procedures and prosthetic devices that support modern medical practice, is also demonstrated in neutropenic patients [17]. Resistance patterns as demonstrated by MRSA rates are similar to other large studies of bloodstream infections [14].

Our data also demonstrate an association between vascular/joint devices, peritoneal dialysis catheters and sepsis associated with both *S. aureus* and the increasingly important hospital pathogen, coagulase-negative staphylococci [13, 18]. These findings have major importance for hospital and particularly ICU practice because of the current widespread reliance upon intravascular and prosthetic devices in seriously ill and immunocompromised patients. On average, patients with staphylococci other than *S. aureus* spent more than 80% of their hospital stay in an ICU. It may be that patients with the risk factors for these organisms spend more time in ICUs or conversely, that a longer duration in an ICU places the patient at risk for sepsis with these organisms. Approximately 1200 patients over a 4-year period had sepsis associated with coagulase-negative staphylococci which emphasizes the need to assess carefully the clinical circumstances when this organism is cultured.

The incidence of candidemia and other fungal infection as a cause of sepsis, although fortunately uncommon, has almost doubled in the last 10 years [19]. When candidemia is detected, a number of risk factors were identified, including the presence of intravascular lines (88%), multiple antibiotics (74%), admission to intensive care (51%), parenteral nutrition (35%), corticosteroid therapy (12%), cancer chemotherapy (11%), renal transplantation (5%) and neutropenia (3%). Our data highlights HIV infection, peritoneal dialysis catheters and other devices as significant risk factors for fungal sepsis. Fungal sepsis in our dataset was associated with the highest mortality and a wide range of organ dysfunction, particularly respiratory and renal. This high mortality rate is consistent with previous reports for individual fungal sepsis and lends support to the general clinical applicability of our database analysis.

Patients who lack a functioning spleen are vulnerable to sepsis caused by bacteria and occasionally protozoa, particularly in childhood and in those who receive immunosuppressive treatment. Overwhelming post-splenectomy infection occurs at an estimated incidence of 0·23–0·42% per year, with a lifetime risk of 5% and the risk seems highest in the first 2 years after splenectomy [20, 21]. The most common pathogen reported to cause overwhelming post-splenectomy sepsis is *S. pneumoniae*, whereas we found in the 63 patients in our study with hyposplenism, sepsis was associated with streptococcal *S. aureus* and fungal infections [22]. Although *S. aureus* has been shown previously to be associated with splenectomy, prophylaxis against this organism is not currently available [23].

In total, 45% of patients with sepsis identified by our ICD-10-AM codes had no causative organisms recorded during their hospital stay. These patients had many risk factors including hepatic failure, insulin-dependent diabetes mellitus, metastatic and non-metastatic cancer, neutropenia and renal failure. Interestingly, vascular/joint infections and HIV infection were rarely associated with sepsis due to an 'unspecified organism' – perhaps indicating a combination of increased sampling and bacteraemia in these circumstances. This group of patients had an average length of stay in an ICU but this would have been influenced by their higher than average mortality. This increased mortality contrasts with the work of Brun-Buisson and colleagues who found no such increase in ICU mortality when an organism was not identified [5].

An important limitation of our study using the VAED administrative dataset was our inability to clinically confirm the timing of the episode of sepsis. The available data permitted only the identification of sepsis using the ICD-10-AM codes from each hospital admission episode, rather than specifically identifying concurrent clinical and physiological parameters such as hypotension and tachycardia that constitute the clinical criteria for sepsis [24]. Nevertheless, the use of ICD codes has been demonstrated to closely approximate the findings of clinical reviews in sepsis research [1, 4]. In addition, the state of Victoria independently and routinely audits the ICD-10-AM coding used in our dataset for accuracy.

In conclusion an Australian administrative dataset, derived from over 3 million hospitalizations, revealed 33 741 cases of sepsis over a 4-year period. Important findings in septic patients were a predominance of Gram-positive bacteria and a considerable utilization of intensive care resources. *S. aureus* was the most common organism isolated and was particularly associated with presence of vascular/joint devices, peritoneal catheters and asplenia. Sepsis was associated with a considerable consumption of hospital resources and an overall mortality of 18%. These findings are similar to European and North American

reports and confirm the substantial burden of sepsis in hospitals.

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