The outcome of patients with sepsis and septic shock presenting to emergency departments in Australia and New Zealand

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ABSTRACT

Background: Early goal-directed therapy might benefit patients with sepsis and septic shock in Australia and New Zealand. However, the current treatment and outcome of these patients is unknown.

Objective: To report the characteristics and outcome of patients with sepsis and septic shock presenting to hospital emergency departments (EDs) in Australia and New Zealand.

Setting: All Australian and New Zealand intensive care units contributing to the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), 1997–2005.

Methods: Patients with an ICU admission diagnosis of non-urinary or urinary sepsis, or non-urinary or urinary sepsis with shock admitted from EDs between 1 January 1997 and 31 December 2005 were identified from the ANZICS APD. Predictor variables for hospital mortality were analysed using logistic regression.

Results: 7649 patients were admitted during the study period. The number of patients admitted per year increased progressively (1997, $n = 368$ [7.7 admissions per ICU]; 2005, $n = 1409$ [14.0 admissions per ICU]). Non-urinary sepsis with shock ($n = 3394$, 44.4%) was the commonest admission diagnosis, and urinary sepsis with shock the least common ($n = 607$, 7.9%). Overall ICU and hospital mortality were 20.9% ($n = 1513/7250$) and 27.6% ($n = 1980/7172$), respectively. Hospital mortality was predicted by hospital type (tertiary, metropolitan, rural or private), patient age, APACHE III score, sepsis classification, mechanical ventilation within the first 24 hours after ICU admission, and calendar year. A significant interaction between sepsis classification and calendar year was demonstrated, with a linear decrease in mortality over time (odds ratio, 0.92; 95% CI, 0.86–0.99; $P = 0.02$).

Conclusions: The reported incidence of sepsis and septic shock in ICU patients presenting to the ED appears to have increased since 1997. In contrast, hospital mortality has decreased. These data require confirmation with a prospective cohort study.

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A recent study in 21 Australian and New Zealand hospitals found that 11.8 per 100 ICU admissions were associated with severe sepsis. In-hospital mortality was 37.5%.[1] Similar incidence and mortality have been reported in other countries.[2-4] In patients with septic shock, the mortality rate approaches 60%.[5,6] Importantly, the incidence of severe sepsis and septic shock appear to have increased over time.[3,6-8]

In 2001, Rivers et al reported an absolute 16% reduction in hospital mortality in patients with severe sepsis and either hypotension or hyperlactataemia presenting to the emergency department (ED) and randomised to receive early goal-directed therapy (EGDT) (compared with standard care).[9] However, significant reservations exist among clinicians regarding the merit of the EGDT "bundle" versus individual components of care. Moreover, the widespread applicability of a single-centre trial with 47% mortality in the control arm is questionable. This concern, and doubt about the robustness of the absolute treatment effect observed in Rivers' study, is reinforced by the substantially lower mortality (28.8%) in a retrospective, observational study of patients with septic shock presenting to the ED of one Australian teaching hospital.[10] The potential impact of EGDT in the Australasian population is, therefore, uncertain.

As a first step to understanding the potential role of EGDT in patients presenting to the EDs of Australian and New Zealand hospitals, and to inform whether formal evaluation with a complex, expensive, controlled trial is feasible and justified, the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) was examined. The aim was to determine the outcome of patients with a medical diagnosis of sepsis or septic shock admitted to the ICU from the ED of Australian and New Zealand hospitals between 1997 and 2005.

Methods

Study design

Prospectively collected ANZICS APD data for a 9-year period from 1 January 1997 to 31 December 2005 were analysed retrospectively. The time frame chosen includes the period of patient enrolment in Rivers' EGDT trial (March 1997 to

March 2000)[9] and provides both contemporaneous and current information on patient outcomes.

All adult patients (⩾ 18 years) admitted to an ICU directly from an ED with the following Acute Physiology, Age, Chronic Health Evaluation (APACHE) III non-operative (ie, medical) diagnostic codes were included in the analysis: non-urinary sepsis, urinary sepsis, non-urinary sepsis with shock, and urinary sepsis with shock (diagnostic codes 501, 502, 503 and 504, respectively). Codes 501 and 502 are derived from the published APACHE diagnostic codes, and codes 503 (non-urinary sepsis with shock) and 504 (urinary sepsis with shock) are additional diagnostic codes modified for the ANZICS APD. Medical patients admitted to an ICU from non-ED sources and operative (ie, surgical) patients admitted directly to an ICU from the operating theatre or recovery room were excluded. Of note, retrospective APD identification of surgical patients with sepsis or sepsis with shock is not possible using APACHE III operative diagnostic codes.

Characteristics of the ANZICS Adult Patient Database

The ANZICS APD is a binational database containing details of patients admitted to an ICU in Australian and New Zealand hospitals.[11] About 72% of all Australian ICUs and 37% of all New Zealand ICUs contribute to the APD (the exact number of contributing ICUs varies between years).[11] In each contributing ICU, data are collected prospectively and entered using standardised software. The database contains information on over 450 000 ICU episodes,[11] including information on the type (elective or emergency surgery or medical) and source of ICU and hospital admission, vital status and destination at ICU and hospital discharge. Variables needed to derive APACHE II and III scores are recorded, and the ICU admission diagnosis is classified according to the APACHE III coding system.[11] Finally, information on ICU and hospital length of stay is documented.

The collection, analysis, and reporting of de-identified data by the ANZICS APD complies with both the Australian legislation (1994) enabling national quality assurance activities and the quality assurance amendment of the *Australian Health Insurance Act 1973*.

Data extraction and statistical analysis

The APD was interrogated for the period January 1 1997 to December 31 2005 inclusive, using commercially available software (SAS, SAS Institute, Cary, NC, USA). The patient cohort was constructed by restricting the "ICU admission source" field to patients admitted from the ED and restricting the "admission diagnostic code" field to the non-operative diagnostic codes 501, 502, 503 and 504. This cohort comprises the eligible patients. Data extraction included information on:

- patient demographic characteristics (age, sex, and APACHE II and III scores);
- hospital type (tertiary, metropolitan, rural or private);
- lead time (time from hospital to ICU admission);
- requirement for invasive mechanical ventilation in the first 24 hours after ICU admission;
- ICU and hospital length of stay; and
- ICU and hospital mortality.

Variables were reported as mean (standard deviation [SD]) unless otherwise indicated. For summarising variable time change, simple non-parametric trend tests were used, with statistical significance ascribed at $P < 0.05$. Categorical variables were analysed using the χ^2 test.

Stata version 9.2 MP (Stata Corporation, College Station, Tex, USA) and S-Plus version 7 (Insightful Corporation, Seattle, Wash, USA) statistical software were used for statistical analysis.

Hospital mortality was modelled using logistic regression with standard errors adjusted: for clustering on ICUs on the basis that, within a cluster, observations were not independent; and by using robust variance estimates to allow for any serial correlation of observations over time.[12] The continuous variables used in the data set were age, severity of illness score (APACHE III) and calendar year. The predictive effect of these variables was entered initially as both linear and simple quadratic terms; more complex non-linear forms were not considered. Candidate categorical predictors were parameterised as simple indicator variables (for example, scored as 0 or 1 for binary variables). Clinically meaningful combinations of variables and their interactions were assessed in the logistic regression model. To preserve clinical transparency, higher order interactions were explored, but not included in the final model. The potential for multiple collinearity was tested using the variance inflation factor (VIF) and condition number (CN), where VIF < 10 and CN < 30[13] are desirable. For reporting, the variables age, severity of illness scores and calendar year were centred (ie, referenced to the mean values).[14]

Model adequacy was gauged by:

- progressive reduction in the Akaike information criterion (AIC) and Bayesian information criterion (BIC),[15] both of which are penalised (with respect to number of observations and model parameters) likelihood methods for model determination;
- traditional criteria of discrimination (receiver operating characteristic [ROC] curve area)[16] and calibration (Hosmer–Lemeshow [H-L] statistic);[17]
- calculation of the model χ^2 for each parameter[18] to adjudge its relative "importance" (after Knaus et al[19]), albeit the final model, using cluster/robust variance adjustments, did not strictly support likelihood ratio tests.

Table 1. Number of patients and intensive care units included in the study

Year	Admissions*	Contributing ICUs†	Admissions per ICU‡
1997	368	48	7.7
1998	323	47	6.9
1999	291	46	6.3
2000	563	62	9.1
2001	872	76	11.5
2002	1059	91	11.6
2003	1282	95	13.5
2004	1483	102	14.5
2005	1411	101	14.0

* Patients with non-urinary sepsis, urinary sepsis, non-urinary sepsis with shock or urinary sepsis with shock admitted to Australian and New Zealand emergency ICUs from emergency departments and reported to the Australian and New Zealand Intensive Care Society Adult Patient Database.
† Total number of ICUs contributing patients to the study cohort.
‡ Number of admissions to ICU each year divided by the number of contributing units for the same year. ◆

At best, these χ^2 values are interpreted heuristically. The final ("full") model was developed on a training set (80% of data) and validated on a determination set (20% of data), the random samples being stratified by calendar year. Mortality probabilities and 95% confidence intervals (CIs) were generated from the final model with continuous covariates centred, and categorical covariates held at the reference category. Graphic displays were generated using the parameter estimates obtained from the full model. A model was also developed using data from those ICUs contributing data in every calendar year of the study ("restricted" model).

To further investigate potential heterogeneity of mortality effect,[20] the final parsimonious model was re-estimated using a two-level (patients within ICUs) random effects logistic regression model ("random effects") with both random intercepts and coefficients, using the "glme" module in the S-Plus statistical package; allowance for an autoregressive-1 (AR1) serial correlation between sequential observations was also tested.[21] Model selection was again guided by information criteria,[22] and model adequacy was assessed by residual analysis and the requirement of normality of the random effects.[23] Parameter estimates were compared with those of the conventional logistic regression: heterogeneity was expressed as the SD (equivalent to variance, on the logit scale) of the specific random-effects parameter.

Results

The number of Australian and New Zealand ICUs contributing data on the study cohort to the ANZICS APD increased progressively over the 9-year study period. Forty-eight ICUs provided data on eligible patients in 1997, and 101 ICUs in 2005 (representing 82.1% of all Australian and New Zealand ICUs contributing data to the APD in 2005). Eighteen ICUs contributed data ($n = 2216$ patient records) to every calendar year of the study.

Table 2. Patient demographic characteristics, by diagnostic code

Variable	All patients* ($n = 7649$)	Sepsis, non-urinary* ($n = 2617$)	Sepsis, urinary* ($n = 1031$)	Shock, non-urinary* ($n = 3394$)	Shock, urinary* ($n = 607$)
Admissions (%)	100%	34.2%	13.5%	44.4%	7.9%
Age (years) (mean [SD])	60.2 (18.1)	58.6 (18.7)	65.9 (16.4)	59.9 (18.1)	67.0 (18.1)
Sex, male (%)	54%	57%	46%	50%	45%
APACHE III score (mean [SD])	74.0 (34.7)	62.1 (31.2)	62.9 (27.6)	86.1 (35.6)	77.8 (31.9)
Lead time (hours) (median [IQR])	4.5 (6.6)	4.9 (6.3)	5.7 (7.2)	4.0 (6.5)	5.1 (7.3)
Ventilation (%)†	34%	23%	16%	48%	30%
ICU length of stay (days)					
Mean (SD)	5.1 (8.2)	4.2 (7.5)	3.5 (5.3)	6.3 (9.1)	5.3 (8.1)
Median (IQR)	2.5 (4.5)	2.1 (3.6)	1.9 (2.9)	2.9 (6.1)	2.7 (4.5)
Hospital length of stay (days)					
Mean (SD)	16.3 (20.8)	15.9 (19.9)	14.2 (16.7)	17.3 (22.6)	16.0 (20.5)
Median (IQR)	9.8 (15.3)	9.7 (13.6)	9.1 (11.8)	10.1 (18.8)	9.8 (14.0)
ICU mortality (%)	20.9%	11.8%	7.5%	32.6%	17.1%
Hospital mortality (%)	27.6%	18.4%	13.8%	39.5%	24.8%

* Diagnostic codes: all patients = 501, 502, 503, 504; sepsis, non-urinary = 501; sepsis, urinary = 502; shock, non-urinary = 503; shock, urinary = 504.
† Ventilation = invasive mechanical ventilation in the first 24 hours after ICU admission. SD = standard deviation. IQR = interquartile range. ◆

Table 3. Crude mortality by calendar year (1997–2005) for patients with non-urinary sepsis, urinary sepsis, non-urinary sepsis with shock and urinary sepsis with shock combined

Calendar year	ICU mortality*	Hospital mortality†
1997	27.4% (96/351)	35.6% (124/348)
1998	29.1% (87/298)	37.7% (113/301)
1999	22.6% (60/266)	30.7% (80/261)
2000	27.8% (148/534)	35.2% (184/522)
2001	23.3% (196/840)	31.6% (256/809)
2002	21.7% (219/1011)	28.1% (280/994)
2003	19.7% (241/1223)	25.8% (311/1209)
2004	18.5% (260/1403)	24.9% (350/1403)
2005	15.6% (207/1324)	21.2% (281/1325)

* For ICU mortality, total number of patients = 7250 (data not available for 399 patients [5.2%]).
† For hospital mortality, total number of patients = 7172 (data not available for 477 patients [6.2%]). ◆

Incidence of sepsis and septic shock

A total of 7649 patients were admitted to an ICU from an ED with an APACHE III diagnosis of non-urinary sepsis, urinary sepsis, non-urinary sepsis with shock, or urinary sepsis with shock during the study period; these represented 6.6% of all admissions to an ICU from an ED (7649/116 006 admissions) and 1.6% of all admissions to an ICU irrespective of admission source (7649/466 266 admissions).

The number of patients admitted each year in the study cohort increased progressively over the same period, with 368 admissions in 1997 (equating to 7.7 admissions per contributing ICU) and 1411 admissions in 2005 (equating to 14.0 admissions per contributing ICU) (Table 1). Most patients ($n = 3435$, 44.7%) were admitted to a tertiary ICU, and 2199 (28.7%), 1466 (19.2%) and 549 (7.2%) were admitted to metropolitan, rural and private hospital ICUs, respectively.

Patient characteristics and outcomes

Fifty-four percent of the study cohort were male ($n = 4113$). APACHE II and III scores on ICU admission were 21.6 (9.6) and 74.0 (34.7), respectively (Table 2). In 34% of patients ($n = 2604$), invasive mechanical ventilation was instituted within the first 24 hours of ICU admission. The time from hospital to ICU admission (lead time) was 4.5 (6.6) hours.

The most common reason for ICU admission was non-urinary sepsis with shock ($n = 3394$, 44.4%), while the least common was urinary sepsis with shock ($n = 607$, 7.9%). Individual admission demographic and patient characteristics and mortality for the four APACHE III diagnostic code groupings are shown in Table 2.

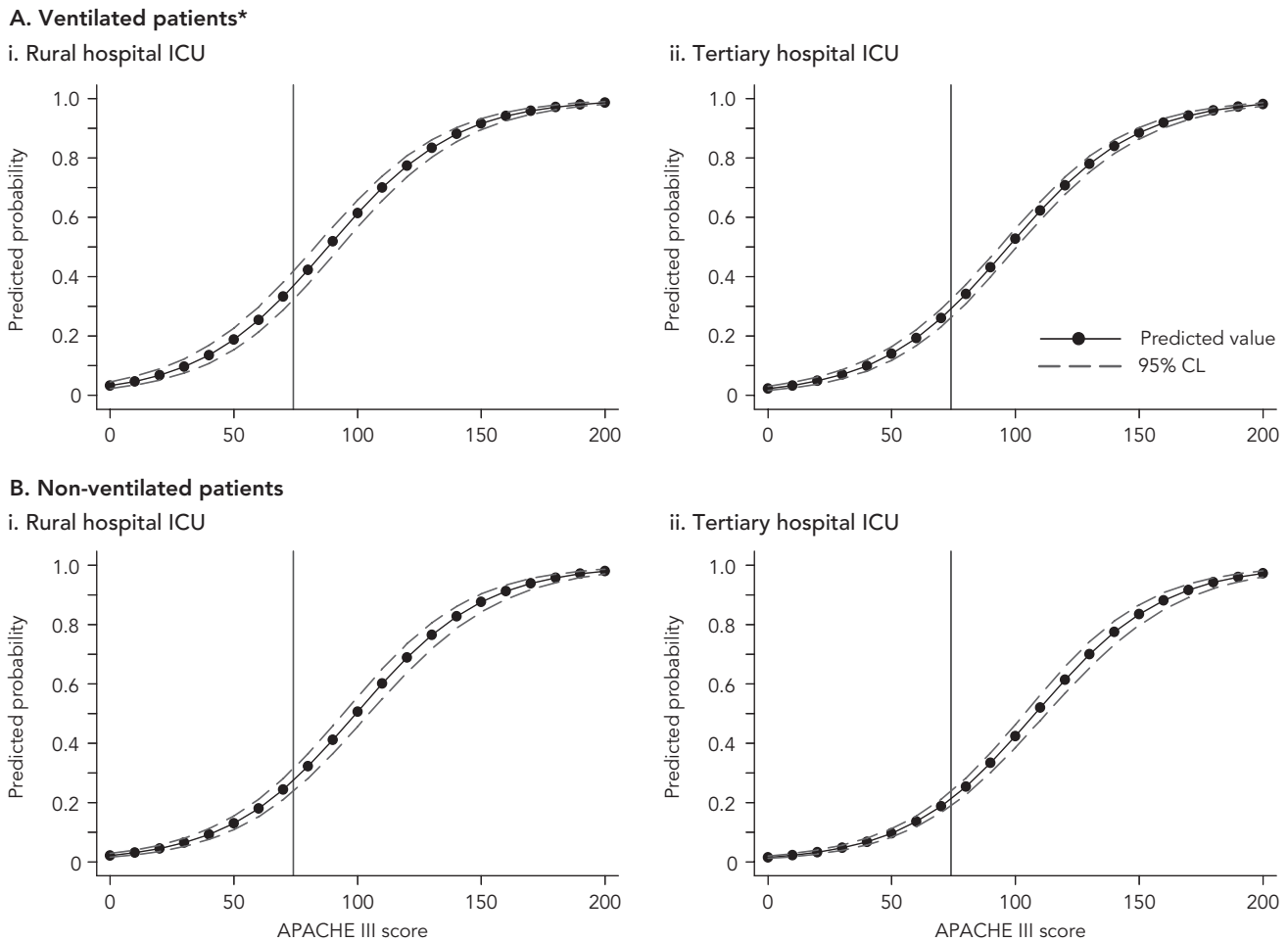
Overall ICU and hospital mortality in the study cohort were 20.9% (1514/7250) and 27.6% (1979/7172), respectively. Crude ICU and hospital mortality by calendar year are shown in Table 3. Both ICU and hospital mortality decreased significantly over time ($P = 0.008$; non-parametric trend test).

Table 4. Predictor variables for hospital mortality

	Full model				Restricted model			Random effects model		
Variable	Estimate	*P*	95% CI	Model χ^2	Estimate	*P*	95% CI	Estimate	*P*	95% CI
Centred APACHE III score	1.043	< 0.001	1.038–1.048	2009.8	1.036	< 0.001	1.032–1.041	1.044	< 0.001	1.039–1.048
Centred APACHE III score^2	0.999	0.03	0.999–0.999	576.5	0.999	0.28	0.999–1.000	0.999	0.046	0.999–0.999
Centred age (years)	1.026	< 0.001	1.019–1.034	246.9	1.030	< 0.001	1.019–1.043	1.027	< 0.001	1.019–1.035
Centred calendar year	0.975	0.30	0.929–1.023	73.7	0.945	0.046	0.894–0.999	0.969	0.26	0.917–1.024
Shock*	1.786	0.001	1.477–2.159	397.1	1.688	0.003	1.188–2.400	1.879	< 0.001	1.557–2.267
Shock x centred age	0.986	0.008	0.977–0.996	123.4	0.981	0.05	0.963–1.000	0.987	0.005	0.977–0.996
Shock x centred calendar year	0.922	0.02	0.861–0.987	60.4	0.969	0.54	0.876–1.072	0.899	0.002	0.842–0.961
Metropolitan ICU†	0.628	0.001	0.476–0.828	0.4	0.547	0.04	0.311–0.963	0.613	< 0.001	0.460–0.817
Tertiary ICU†	0.674	0.007	0.506–0.899	1.7	0.783	0.44	0.419–1.463	0.720	0.02	0.547–0.947
Private ICU†	0.654	0.01	0.471–0.908	3.9	0.814	0.43	0.488–1.356	0.621	0.02	0.420–0.916
Ventilation‡	1.375	0.001	1.140–1.659	763.7	1.608	< 0.001	1.271–2.034	1.396	0.002	1.135–1.716
Ventilation x lead-time	1.375	0.002	1.120–1.687	253.1	1.191	0.35	0.826–1.718	1.379	0.006	1.097–1.734

* Shock = non-urinary sepsis with shock. Reference category for shock classification was urinary sepsis with shock, urinary sepsis and non-urinary sepsis (combined).
† Reference category for hospital type was rural ICU. ‡ Ventilation = invasive mechanical ventilation in the first 24 hours after ICU admission.
APACHE = Acute Physiology, Age, Chronic Health Evaluation. ◆

Figure 1. Predicted mortality curves for patients with a diagnosis of non-urinary sepsis with shock (age fixed at 60 years)

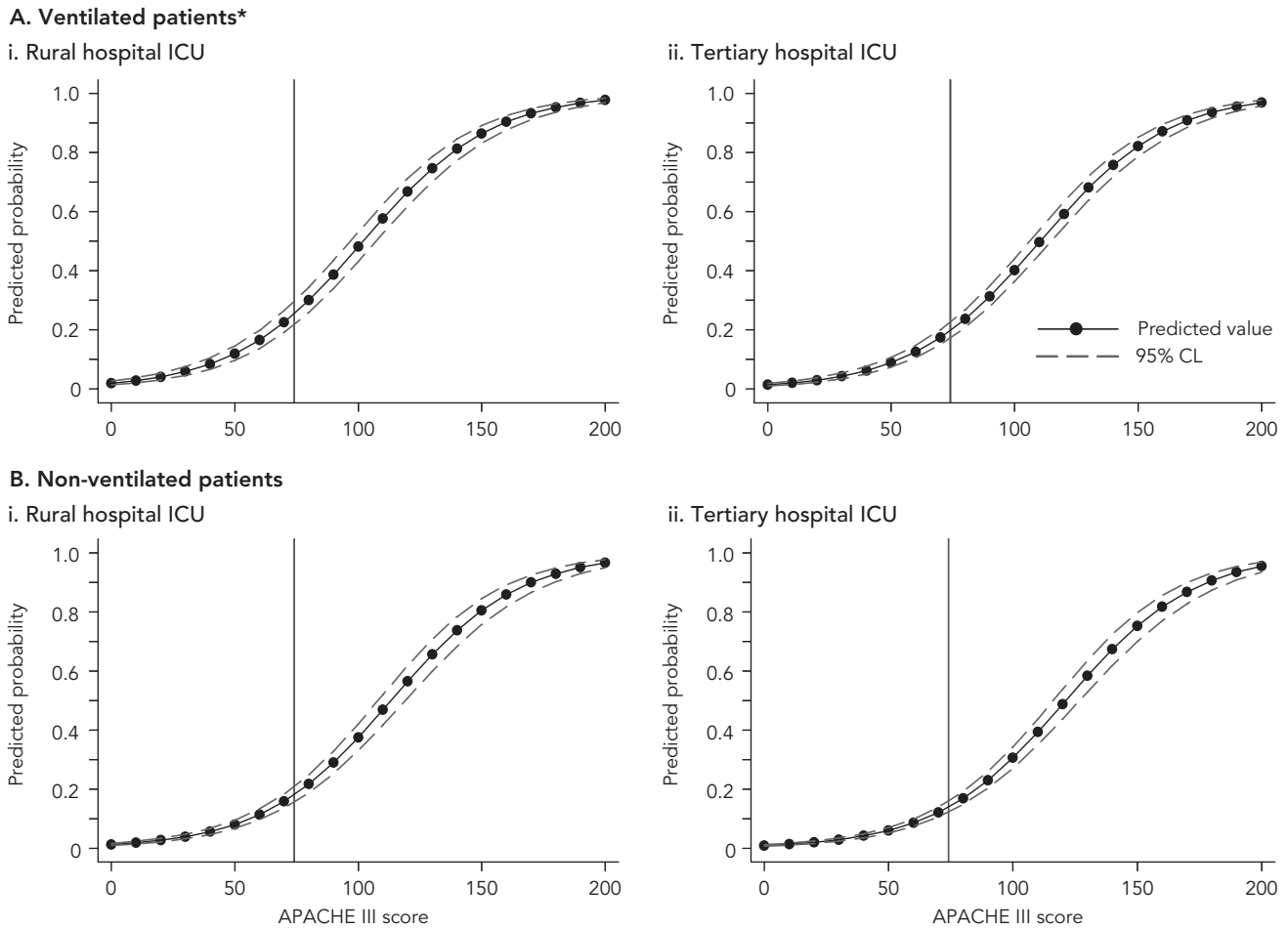


* Ventilated = invasive mechanical ventilation in the first 24 hours after ICU admission.
Solid vertical line represents the mean APACHE III score of the overall study cohort (74.0). CL = confidence limit. ◆

Parameter estimates for the three models (full, restricted and random effects; see *Statistical analysis* above) predicting hospital mortality are shown in Table 4. Modest collinearity was evident with non-centred continuous variables (VIF, 5; CN, 24.9), but this was ameliorated by centring (VIF, 1.7; CN, 11.7). The developmental-set model had an H-L statistic with $P = 0.12$ and ROC area, 0.86, while the validation-set model had an H-L statistic with $P = 0.42$ and ROC area, 0.86. Estimates were therefore generated on the whole data set (full model) with an H-L statistic $P = 0.37$ and ROC area, 0.86.

Increasing age and severity of illness (as determined by APACHE III score) were predictive of increased mortality, with a mild quadratic effect of the APACHE III score. Mechanical ventilation was also associated with increased mortality, as was the interaction between ventilation and lead time (analysed as a binary variable $\leqslant$ or >4.5 hours). No significant differences were demonstrated between the "urinary sepsis with shock", "non-urinary sepsis" and "urinary sepsis" patient sets with respect to hospital mortality ($P \geqslant 0.1$); ICU admission category was therefore analysed as a binary variable (urinary sepsis with shock, non-urinary sepsis and urinary sepsis combined compared with non-urinary sepsis with shock). Not surprisingly, non-urinary sepsis with shock was a significant predictor of mortality (odds ratio [OR] point estimate, 1.786). Predicted mortality curves for the non-urinary shock and the remaining combined diagnostic code patient sets at a fixed (mean) age for both ventilated and non-ventilated patients are shown in Figure 1 and Figure 2, respectively. Metropolitan, tertiary and private ICUs showed lower mortality risk than rural ICUs, but no differences were evident between these three

Figure 2. Predicted mortality curves for patients with a diagnosis of urinary sepsis with shock, urinary sepsis and non-urinary sepsis combined (age fixed at 60 years)



* Ventilated = invasive mechanical ventilation in the first 24 hours after ICU admission.
Solid vertical line represents the mean APACHE III score of the overall study cohort (74.0). CL = confidence limit. ◆

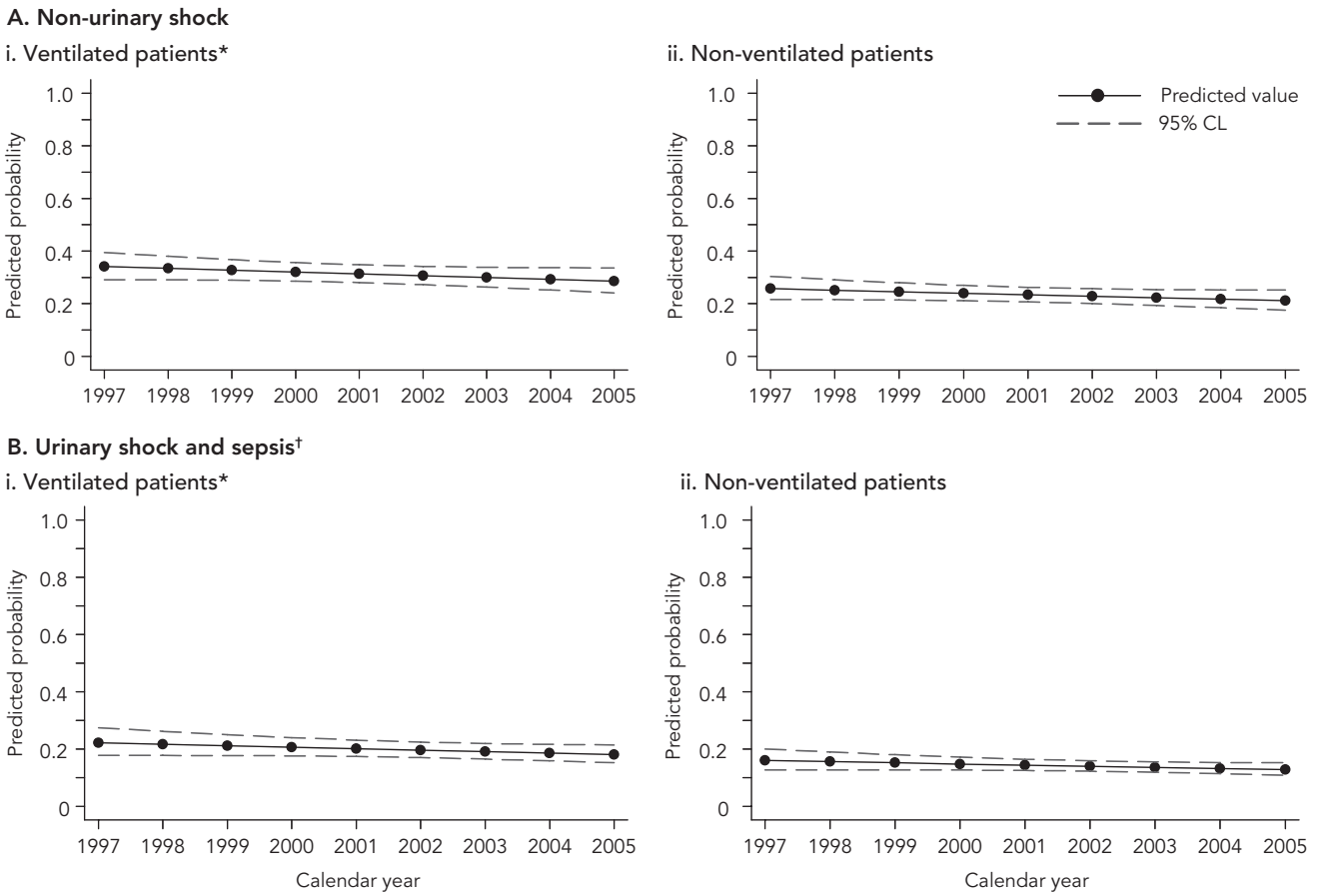
hospital categories ($P \geqslant 0.56$). Thus, for a (mean) APACHE III score of 74.0, predicted hospital mortality for ventilated and non-ventilated non-urinary shock patients in a tertiary hospital ICU (Figure 1, top and bottom right panels) was approximately 30% and 21%, respectively. In contrast, predicted hospital mortality for ventilated and non-ventilated patients in a rural hospital was approximately 38% and 28%, respectively. Figure 2 illustrates similar APACHE III mortality differential effects for the remaining three sepsis diagnostic code patient sets.

A small decrease in mortality with time was present (calendar year alone considered as a continuous variable and modelled linearly [main effects OR, 0.935; 95% CI, 0.900–0.971]). However, this effect was modified (OR, 0.976; 95% CI, 0.929–1.023) due to an interaction with "shock" status, such that the modest decrease in mortality was located in the "non-urinary sepsis with shock" patient subset. The interaction between ICU admission category and calendar year is seen in Figure 3 (OR, 0.922; 95% CI, 0.861–0.987; $P = 0.02$; [mean] age and APACHE III score fixed) with a marginally steeper mortality curve slope in the non-urinary shock subset (Figure 3, bottom panels) compared with the remaining three sepsis diagnostic code patient sets combined (Figure 3, top panels).

The scalar values of the model χ^2 suggested that the most determinate variables were severity of illness score, mechanical ventilation and shock status (Table 4).

When the data set was restricted to ICUs that contributed continuously over the study period (restricted model), similar parameter estimates were seen (Table 4; H-L statistic $P = 0.81$, ROC area, 0.85), although the individual predictors showed variability of P values with respect to nominal 0.05 signifi-

Figure 3. Predicted effect of calendar year on hospital mortality according to diagnostic category (reference calendar year 2001 and fixed covariates: age 60 years, APACHE III score 74.0, and tertiary hospital ICU)



* Ventilated = invasive mechanical ventilation in the first 24 hours after ICU admission.
† Urinary sepsis with shock, urinary sepsis and non-urinary sepsis combined. CL = confidence limit. ◆

cance levels, presumably due to the reduced sample size. The decline in mortality over time was still present (OR for calendar year as a continuous variable, 0.945; $P = 0.046$).

The random effects model demonstrated modest statistical advantage compared with (pooled) logistic regression — both as a random intercept model (separate intercepts for each ICU) and as a random coefficient model (separate intercepts and slopes of effect across ICUs for APACHE III score, ventilation, age and calendar year). The latter model was the most advantageous in terms of AIC and BIC; although the fixed effects were consistent with those of the pooled effects logistic regression model (Table 4, random effects model). Maximum heterogeneity (assessed by the SD of the random effects parameters) was evident at the level of "ventilation" (SD, 0.023; 95% CI, 0.07–0.78), "shock" (SD, 0.37; 95% CI, 0.22–0.61) and calendar year (SD, 0.12; 95% CI, 0.08–0.20), whereas heterogeneity of the APACHE III and age effect was minimal (point estimates, 0.005 and 0.003, respectively). The residual heterogeneity of the preferred random coefficient model was modest at 0.22. However, the predicted probabilities of this model generated an ROC curve area of 0.88 and an H-L statistic $P = 0.35$; the ROC curve area was superior ($P < 0.001$) to that of the fixed effects estimate, 0.86. Allowance for an AR1 correlation between sequential observations was again advantageous (likelihood ratio test $P = 0.02$), and the ROC curve area was judged statistically superior to the random coefficient model without an AR1 correlation (0.877 versus 0.876, $P = 0.001$). However, this statistical advantage was presumably a function of the large sample size.[24]

Discussion

Using the ANZICS APD, the incidence, features and outcome of sepsis and septic shock in patients admitted to the

Table 5. Patient demographic and outcome data for the ANZICS APD study cohort and the Early Goal Directed Therapy trial patient cohorts[9] (mean [SD] unless otherwise indicated)

	APD (1997–2005)*	EGDT trial (1997–2000)†	
		Control	Treatment
Total no. of patients	7649	133	130
Patients with shock (% [*n*])	52.3% (4001)	51.3% (68)	54.7% (71)
Age (years)	60.8 (18.1)	64.4(17.1)	67.1 (17.4)
Sex male (% [*n*])	53.9% (4113)	50.4% (67)	50.8% (66)
Medical (% [*n*])	100% (7649)	93.3% (124)	90.6% (118)
APACHE II score‡	21.6 (9.6)	20.4 (7.4)	21.4 (6.9)
APACHE III score	74.0 (34.7)	na	na
Lead time (h)	4.5 (6.6)	6.3 (3.2)	8.0 (2.1)
Hospital length of stay (days)	16.3 (20.8)	13.0(13.7)	13.2 (13.8)
Hospital mortality (% [*n*])			
All patients	27.7% (1980)§	46.5% (62)	30.5% (40)
Patients with shock	36.2% (1403)§	56.8% (40)	42.3% (29)

* Diagnostic codes 501 to 504 inclusive (non-operative urinary or non-urinary sepsis or sepsis with shock) with the emergency department as the source of ICU admission.
† 1997–2000 represents the study period for the EGDT trial.
‡ For the ANZICS APD, APACHE II score was derived from the worst physiological variables in the 24 hours after ICU admission. For the EGDT trial, APACHE II score was derived from the worst physiological variables at study entry in the emergency department.
§ For hospital mortality, data were available for 7172 and 3876 patients for total patients and patients with shock, respectively.
ANZICS APD = Australian and New Zealand Intensive Care Society Adult Patient Database.
EGDT = early goal-directed therapy. na = not available. ◆

ICU after presentation to the ED was investigated for the purpose of assessing the feasibility of conducting a randomised, controlled trial of EGDT in Australia and New Zealand. The important findings are:

- The number of patients admitted to the ICU from the ED with sepsis and septic shock in contributing hospitals increased over the period 1997 to 2005;
- There appears to be a sufficient number of potentially eligible patients to allow recruitment into a large, randomised trial;
- Mortality of ED patients with sepsis and septic shock declined progressively over the study period in contributing hospitals; and
- The likely hospital mortality in the control arm in a phase III trial may be $\leqslant 30\%$.

Mortality in sepsis and septic shock is reportedly high, ranging between 30.8% and 62.5%.[2-4] In our study, overall hospital mortality was 27.6%. Not surprisingly, an incremental relationship between age, severity of illness (as assessed by APACHE III score) and hospital mortality was demonstrated. It is also plausible that patients requiring ventilation in the first 24 hours after ICU admission (an independent risk factor for mortality) have increased mortality with prolonged ED length of stay (lead time > 4.5 hours). Although mortality for patients admitted to ICUs in rural hospitals was higher than mortality for ICUs in other geographical locations, regional and geographical differences in outcome are presumably a surrogate for the allocation of human and material resources.

Over the 9-year study period, there was a gradual decline in hospital mortality. In 2005, observed mortality was 21.2%, versus 35.6% in 1997. Martin et al reported a similar decline in hospital mortality for sepsis patients in the United States ($n = 10\,319\,418$) over a 22-year period, averaging 27.8% in 1979–1984 and 17.9% in 1995–2000.[8] A systematic review of 131 clinical studies published between 1958 and 1997 also demonstrated a significant decrease in mortality over time.[25] More recently, the EPISEPSIS study reported that hospital mortality from severe sepsis in French ICUs decreased over the past decade (59% in 1995 versus 41.9% in 2001).[3,7] Our finding of declining mortality for patients with sepsis and septic shock is consistent with the published literature. Any future studies of EGDT will, therefore, need to consider this decline when calculating sample sizes. Of note, the interaction between diagnostic code and calendar year suggests that the outcome benefit was primarily related to improved survival in the non-urinary shock subset — the group to whom, arguably, the greatest research and therapeutic endeavours have been directed.

In 2001, Rivers et al reported that early resuscitation targeted to a set of physiological goals (EGDT) resulted in a significant reduction in mortality in patients with severe sepsis.[9] Two hundred and sixty-three patients presenting to the ED of a single centre in the US over a 3-year period were randomised to receive either standard therapy or protocolised goal-directed therapy during the first 6 hours in the ED. EGDT was associated with a significant reduction in both all-cause hospital mortality (30.5% versus 46.5% for the control group) and 60-day mortality (44.3% versus 56.9% for the control group).

Notwithstanding the impressive 16% absolute reduction in hospital mortality, the question remains whether the results of this single-centre trial are generalisable to similar patients presenting to EDs in Australia and New Zealand. The results of single-centre trials continue to influence clinical practice. Most notable in the critical care literature in recent years is the randomised trial of intensive insulin therapy in surgical patients in a Belgian hospital,[26] the

subsequent recommendation for tight glycaemic control in the 2004 Surviving Sepsis Campaign guidelines,[27] and the adoption of tight glycaemic control in 31% (12/39) of Australian and New Zealand ANZICS Clinical Trials Group-affiliated ICUs.[28] However, a German multicentre trial of tight glycaemic control in patients with severe sepsis was recently terminated prematurely because of an increased risk of severe hypoglycaemia without any evidence of a survival benefit (mortality, 21.9% in the conventional group versus 21.6% in the intensive insulin therapy group, $P = 1.0$), thus highlighting the concerns regarding single-centre studies.[29,30]

Single-centre studies reflect a local (and sometimes unique) structure of care. As such, applicability and generalisability of trial results to the broader patient population depend on a number of factors, including the type of patient selected for inclusion or exclusion, the type of treatment tested, the end-points studied and the health care setting. In the absence of evidence from randomised, controlled trials, assessment of the external validity of the Rivers' trial to the Australia and New Zealand region is limited. The issue of generalisability may, in part, be elucidated by comparing the control and EGDT patient groups in the Rivers' trial with the patient cohort in the current study (Table 5). While formal comparison is not possible, it is interesting to note that patients in the ANZICS APD are of similar age, male-to-female ratio and severity of illness (as determined by APACHE II score) as those enrolled in the Rivers' study, albeit the method of APACHE II score calculation was different. In the ANZICS APD, the score is calculated from the worst physiological variables in the first 24 hours after ICU admission, while in the Rivers' trial the APACHE II score was derived from baseline data at time 0 hours. The percentage of patients with shock in the current ANZICS APD study cohort is also similar to that in the EGDT trial (52.5% versus 51.3% and 54.7% for the EGDT control and treatment groups, respectively).

However, despite apparently similar baseline patient demographic characteristics, hospital mortality was lower than that in the control arm of Rivers' study both for the overall APD study cohort and for patients admitted to the ICU with an APACHE III diagnosis of either urinary or non-urinary septic shock. Overall hospital mortality was also lower than in the treatment group receiving EGDT (Table 5). Notably, other studies investigating the effect of adjunctive therapies in patients with severe sepsis have reported similar control-arm mortality to that in the current APD cohort study. Twenty-eight-day all-cause mortality in the recombinant human activated protein C and antithrombin III multicentre trials were 30.8% (71.7% baseline incidence of shock)[31] and 38.7% (43.2% baseline incidence of shock),[32] respectively.

The current study has a number of limitations. Although the ANZICS APD involves prospective data collection, retrospective analysis introduces the potential for patient misclassification. Specifically, patients with sepsis or septic shock may have been assigned other diagnostic codes as the reason for ICU admission: in particular, diagnostic codes related to the primary pathology (eg, bacterial pneumonia or cellulitis). However, a recent report on the quality of the APD assessed according to criteria of the Directory of Clinical Databases indicated that the overall quality level achieved by the APD was high across all 10 criteria.[11]

Another limitation is that not all Australian and New Zealand ICUs contribute to the database. About 61.9% of potentially eligible ICUs provide data to the APD, including 82.4% of Level III public hospital ICUs (the exact number of contributing units varies from year to year).[11] However, not all of the potentially eligible ICUs have an associated ED. It should also be noted that those units that do contribute to the APD are self-selected and not necessarily representative of the whole population. Nonetheless, they are more likely to be representative of overall system performance than a single hospital and provide the largest and most comprehensive assessment of system performance in this field yet reported.

Finally, for ICU and hospital mortality, outcome data were not available in 5.2% (399/7649) and 6.2% (477/7649) of patients, respectively. However, because of the large sample size, the missing data are unlikely to significantly influence the study results. Moreover, the study can draw no conclusions regarding surgical or postoperative patients admitted to the ICU with sepsis or septic shock.

Conclusions

This retrospective analysis of the ANZICS APD involving over 7000 patients admitted to an ICU from an ED suggests that the incidence of sepsis and septic shock increased between 1997 and 2005. In contrast, hospital mortality decreased over the same period. Both calendar year and severity of illness (as indicated by APACHE III score, the presence of shock and requirement for mechanical ventilation) were predictors of hospital mortality. Importantly, the study findings indicate that the mortality of patients currently presenting with sepsis or septic shock to the EDs of Australian and New Zealand hospitals may be considerably lower than that observed in the Rivers' EGDT trial. Although the results of our analysis need to be confirmed in a prospective study, they represent the first step in understanding the role or applicability of EGDT in such patients.

Future studies

A 3-month, prospective, multicentre observational survey of patients presenting to the ED with severe sepsis or septic shock in over 30 Australian and New Zealand hospitals is currently being undertaken by the ANZICS Clinical Trials Group in collaboration with the Australian and New Zealand Intensive Care Research Centre. The results, combined with the current APD analysis, will provide crucial information for the design of a prospective, randomised, multicentre trial of EGDT.

The apparent declining mortality rate necessitates conservative sample size calculations. Assuming a relative risk reduction similar to the 22% reduction in 60-day mortality reported by Rivers et al, about 1500–2000 patients (80% and 90% power, respectively) would need to be randomised to test the hypothesis that EGDT decreases mortality.

> At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use.
>
> Austin Bradford Hill, 1984.[33]

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