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## A comparison of characteristics and outcomes of patients admitted to the ICU with asthma in Australia and New Zealand and United states

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### ABSTRACT

**Objective:** To compare the characteristics, use of invasive ventilation and outcomes of patients admitted with critical asthma syndrome (CAS) to ICUs in Australia and New Zealand (ANZ), and a large cohort of ICUs in the United States (US). **Methods:** We examined two large databases of ICU for patients admitted with CAS in 2014 and 2015. We obtained, analyzed, and compared information on demographic and physiological characteristics, use of invasive mechanical ventilation, and clinical outcome and derived predictive models. **Results:** Overall, 2202 and 762 patients were admitted with a primary diagnosis of CAS in the ANZ and US databases respectively (0.73% vs. 0.46% of all ICU admissions,  $P < 0.001$ ). A similar percentage of patients received invasive mechanical ventilation in the first 24 h (24.7% vs. 24.4%,  $P = 0.87$ ) but ANZ patients had lower respiratory rates and higher PaCO<sub>2</sub> levels. Overall mortality was low (1.23 for ANZ and 1.71 for USA;  $P = 0.36$ ) and even among invasively ventilated patients (2.4% for ANZ vs. 1.1% for USA;  $P = 0.38$ ). However, ANZ patients also had longer length of stay in ICU (43 vs. 37 h,  $P = 0.001$ ) and hospital (105 vs. 78 h,  $P = 0.003$ ). **Conclusions:** Patients admitted to ANZ and USA ICU with CAS are broadly similar and have a low and similar rate of invasive ventilation and mortality. However, ANZ patients made up a greater proportion of ICU patients and had longer ICU and hospital stays. These findings provide a modern invasive ventilation and mortality rates benchmark for future studies of CAS.

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## Introduction

Critical asthma syndrome (CAS) is defined as a severe and sudden respiratory condition that, although needing aggressive and urgent treatment, has not progressed to irreversible hypoxia and cardio-pulmonary arrest [1]. CAS appears to be a relatively uncommon problem in the ICU [1–3] with a previously estimated prevalence of between 1.1 and 1.7% of all ICU admissions [4–6]. However, about 8% of patients admitted to hospital with an exacerbation of asthma require ICU admission [7]. The incidence of CAS appears to be decreasing in Australia and New Zealand (ANZ) and in the United States of America (USA) [6,8,9]. However, there has been no direct comparison between these two different healthcare systems in

relation to the prevalence, invasive ventilation rate, and outcome of patients admitted to intensive care with CAS. This is undesirable because such a comparison and such data would provide an important contemporary benchmark for future interventional studies, define what outcomes can be realistically studied and modified by interventional trials, allow the more accurate statistical powering of such studies, define a realistic recruitment rate, and provide useful public health information. Until the advent of large electronic data sets, however, such information had been missing. Such data sets, however, are now potentially available.

Two large electronic databases for ICU admissions with CAS were obtained for analysis: the Australian

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and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) [10], and the eICU Collaborative Research Database (CRD) from the USA [11].

Using these two databases, we aimed to describe the prevalence, characteristics, invasive mechanical ventilation rates, and outcomes of patients with CAS and to test the hypothesis that, compared with the USA healthcare system with its inherent differences (including absent universal health insurance) [12,13], Australia and New Zealand ICUs may admit patients with asthma who have significantly different characteristics and outcomes.

## Methods

This is an observational, analytic, cohort-based study.

We extracted de-identified episode data (names and hospital record numbers were removed from the database before analysis) of asthma admissions to ICU during 2014 and 2015 from two databases. The first is the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) [10], which is a large bi-national clinical database containing de-identified data from all ICU admissions at participating sites. In 2014/2015, data were available from 163 ICUs that contributed to the ANZICS APD, of these 158 ICUs reported at least one admission due to asthma. The second is the eICU Collaborative Research Database (eICU-CRD), which is a large clinical database populated with de-identified patient data from 335 ICUs at 208 hospitals monitored by tele-ICUs in 2014 and 2015. The eICU-CRD is a representative sample of the Philips eICU Research Institute database that has been donated by Philips Healthcare for public access and is described in detail at <https://eicu-crd.mit.edu> [11].

Data in the ANZICS APD were submitted directly from participating sites to the ANZICS Centre for Outcome Evaluation (CORE). De-identified data are made available by ANZICS for research use subject to local hospital ethics approval. Ethical approval for the use of such data for this study was granted by the Alfred Hospital Ethics committee (number 366/17).

Data in the eICU-CRD was either directly documented or interfaced via Health Level-7 (HL7) standards into the clinical information system used to remotely monitor tele-ICU patients across the United States. Use of such data is exempt from institutional review board oversight as the security schema, which was analyzed, and re-identification risk, which was certified (45 Code of Federal Regulations 164.514(b)

(1) and 45 C.F.R. 164.514(b) (1)(i); Health Insurance Portability and Accountability Act Certification no. 80503C) were able to meet safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2).

Patients aged 15 years and older and admitted to ICU with an Acute Physiology and Chronic Health Evaluation (APACHE) diagnosis of asthma were included. Both the total cohorts of asthma patients, as well as the subgroup of asthma patients requiring endotracheal intubation were compared. Data from any subsequent re-admissions to ICU for that same hospital admission episode was excluded. Patients who were identified as having had a cardiac arrest, a respiratory arrest, or a cardio-pulmonary arrest in the 24 h before ICU admission are reported for the ANZ cohort but were excluded from comparative analysis because such patients were only identified in the ANZ dataset and not in the USA data set and because they do not fall within the classical definition of CAS [1].

The following physiological variables were extracted during the first 24 h in the ICU: highest heart rate HR; highest non-ventilated respiratory rate RR; lowest arterial oxygen tension ( $\text{PaO}_2$ ) and pH, and highest arterial carbon dioxide tension ( $\text{PaCO}_2$ ) from arterial blood gas.

## Statistical analysis

Data were analyzed using Microsoft Excel for Mac v15.32 (Microsoft Corporation, Redmond, Washington); Stata version 13.1 (StataCorp., College Station, Texas, United States) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna). Categorical variables are summarized as number (percent) and were compared using the Fisher's exact test. *P* values are reported, as well as relative risks and 95% confidence intervals for significant values. Continuous variables were tested for normality. Due to skewed and non-normal distributions of all continuous data, these are summarized as median (interquartile range). The skewed variables of ICU length of stay, hospital length of stay, body mass index (BMI), and age were log-transformed and tested using the Student's *t*-test and a ratio of geometric means with 95% confidence interval is reported. Continuous variables not suitable for transformation were compared using the Mann-Whitney test with *P* values reported. Multivariable analysis was performed using Cox proportional hazard for ICU and hospital LOS using age, APACHE, sex, GCS, and intubation status. All

statistical tests were two-sided, with a  $P$  values  $<0.05$  considered to indicate statistical significance.

## Results

### Overall cohort

There were 301,747 ICU admissions in the ANZICS APD and 167,438 ICU admissions in eICU databases (Table 1). Proportionately, there were significantly more CAS ICU admissions in the ANZICS APD ICUs than in the USA eICU database (2202 (0.73%) vs. 762 (0.46%), RR 1.6, 95% CI 1.47–1.74,  $P < 0.001$ ).

However, patients with a diagnosis of cardiac or respiratory or combined cardio-respiratory arrest ( $n = 76$ ) in the 24 h prior to ICU admission were only identified as such in the ANZICS APD but not in the eICU cohort.

Among such ANZ patients, 46 were classified as having had a respiratory arrest and 42 of these survived to hospital discharge; 17 were classified as having had a cardiac arrest and 7 survived to hospital discharge, finally 13 were identified as having had a combined cardio-respiratory arrest and 6 survived to hospital discharge (total survivors: 55).

As shown in Table 1, patients admitted with CAS to eICU hospitals, had higher APACHE III scores,  $\text{PaO}_2$ ,  $\text{PaCO}_2$  levels, and respiratory rate. However, they had similar rates of endotracheal intubation (ANZICS 24.7% vs eICU 24.4%,  $P = 0.87$ ), ICU mortality (0.73% vs. 0.79%  $P = 0.81$ ) and hospital mortality (1.23% vs. 1.71%,  $P = 0.36$ ).

When patients with a pre-ICU cardiac arrest were included in this analysis, the hospital mortality rate in the ANZ CAS population increased to 2.18%, but

remained statistically similar ( $P = 0.43$ ) to that of the USA cohort.

In contrast, Australian and New Zealand CAS patients, had longer hospital length of stay LOS (105 vs. 78 h,  $P = 0.003$ ) (Figure 1) and ICU length of stay (LOS, 43 vs. 37 h,  $P = 0.001$ ) (Figure 2)

### Endotracheally intubated cohort

In the endotracheally intubated cohort, compared to eICU cohort, ANZICS APD patients had a similar APACHE III score, but were older (Table 2). ANZICS APD patients receiving invasive mechanical ventilation also had a higher  $\text{PaCO}_2$ , lower pH, lower  $\text{PaO}_2$ , and a lower respiratory rate. Furthermore, they had longer hospital LOS by almost two days. On Cox proportional hazard model for ICU and hospital LOS between the two groups, ANZICS patients had a hazard ratio of 1.24 and 1.29 for longer stay respectively. Age, APACHE III score, female sex, and intubation status were also significant variables affecting LOS (Tables 3 and 4).

## Discussion

### Key findings

We compared CAS patients admitted to two large cohorts of USA vs. ANZ ICUs. We found that baseline demographic features such as age, sex, rate of intubation, ICU, and hospital mortality were similar. However, CAS patients made up a greater percentage of all ICU admissions in ANZ, and despite having lower illness severity scores, they had longer ICU and hospital stays. Moreover, based on APACHE scores,

**Table 1.** Patient characteristics in the ANZICS vs. eICU cohorts.<sup>a</sup>

|                                | ANZICS           | eICU             | $P$ value |
|--------------------------------|------------------|------------------|-----------|
| All ICU admissions             | 301,747          | 167,438          | –         |
| Asthma, $n$ (%)                | 2202 (0.73)      | 762 (0.46)       | $<0.001$  |
| Age (y)                        | 42.5 (30–54)     | 43 (31–56)       | 0.02      |
| Female, $n$ (%)                | 1524 (69.2)      | 524 (68.8)       | 0.82      |
| BMI ( $\text{kg}/\text{m}^2$ ) | 30.1 (24.7–36.2) | 29.8 (24.3–36.9) | 0.47      |
| Intubated, $n$ (%)             | 544 (24.7)       | 186 (24.4)       | 0.87      |
| Died ICU, $n$ (%)              | 16 (0.73)        | 6 (0.79)         | 0.81      |
| Died hospital, $n$ (%)         | 27 (1.23)        | 13 (1.71)        | 0.36      |
| ICU LOS (h)                    | 43 (23–74)       | 37 (21–62)       | 0.001     |
| Hosp LOS (h)                   | 105 (64–174)     | 78 (36–125)      | 0.003     |
| APACHE score                   | 36 (27–47)       | 38 (29–49)       | 0.003     |
| $\text{FiO}_2$                 | 0.4 (0.3–0.5)    | 0.4 (0.35–0.5)   | 0.41      |
| $\text{PaO}_2$ (mmHg)          | 86 (69–128)      | 95 (75–142)      | $<0.001$  |
| pH                             | 7.35 (7.27–7.41) | 7.35 (7.30–7.40) | 0.70      |
| $\text{PaCO}_2$ (mmHg)         | 40 (33–53)       | 45 (38–55)       | $<0.001$  |
| HR (beats/min)                 | 120 (110–133)    | 122 (109–133)    | 0.86      |
| RR (breaths/min)               | 28 (16–35)       | 32 (26–41)       | $<0.001$  |
| MAP (mmHg)                     | 74 (66–108)      | 74 (60–125)      | 0.27      |

Abbreviations: BMI: body mass index; LOS: length of stay; APACHE: Acute Physiology and Chronic Health Evaluation.

<sup>a</sup>All continuous data expressed as medians with interquartile range.

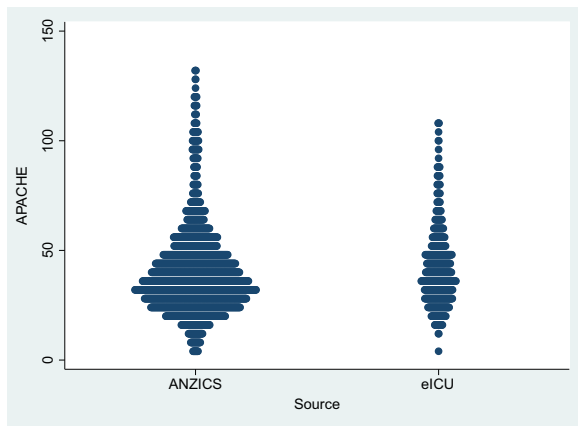


**Figure 1.** Distribution plot of APACHE III scores for the two cohorts.

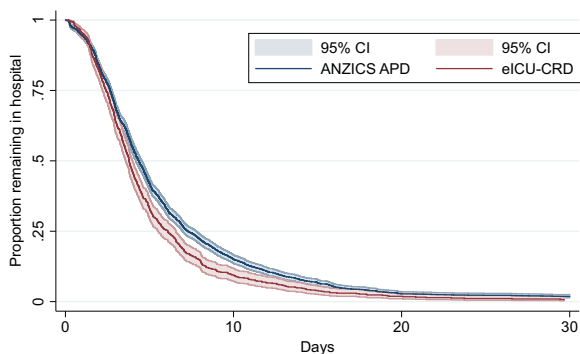


**Figure 2.** Kaplan-Meier plot of time to hospital discharge for the two study cohorts.

USA patients were more severely ill, had higher HR, RR, and  $\text{PaCO}_2$  levels. In contrast, in the intubated cohort, ANZ patients had higher  $\text{PaCO}_2$ , lower RR and pH and also in such patients, ICU stay was longer in ANZ. Among ANZ patients (the only data set with such information) nine out of ten patients with a pre-ICU respiratory arrest survived. Finally, on Cox proportional hazard modeling for both the whole cohort and the intubated cohort, being admitted to an ANZ ICU was independently associated with significantly higher hazard ratios for longer hospital and ICU stay (Figure 3).

### Relationship to previous studies

There has been no previous comparison between ANZ and USA patients admitted to ICU with CAS. However, Australia is known to have a particularly high incidence of asthma [14] compared to other countries. This might have affected the ANZ data as the vast majority of ICUs are located in Australia and might explain the greater prevalence of CAS in ANZ ICUs. Using the ANZ data, which capture close to

90% all ICUs in the two countries, we estimate a contemporary incidence of CAS of approximately 4/million/year. Moreover, given the population of ANZ relative to the combined population of North America and Europe, we estimate that such incidence would translate into approximately 70,000 cases/year in high-income countries. In 2007, Stow et al. [6] reported on declining asthma admissions and mortality in Australia and NZ over time. Compared to that study, we report a further decrease (down from 1.5 to 0.73%), a much lower intubation rate (down from 36.1 to 24.7%), and a lower hospital mortality (down from 3.2 to 2.2%), while the ICU length of stay rose from 38 to 43 h. The reduction in the rate of intubation may reflect increasing use of non-invasive ventilation (NIV) [15–18].

Gupta et al. [4] in 2004 also reported that asthma accounted for 1.7% of admissions in the UK, but with a much higher rate (57%) of mechanical ventilation than in our ANZ or USA data. In Gupta's study, there were also much higher ICU and hospital mortality rates at 7.1 and 9.8%, respectively. This probably reflects improved outcomes in our cohort compared to the above study period of 1995–2001 [6] but also that Gupta's study included patients who had a cardio-pulmonary arrest prior to admission. However, in Gupta's study, patients who received pre-ICU admission CPR accounted for 8% of all admissions compared with 3.5% of all ANZ admissions. Moreover, even when such patients are added to the ANZ cohort outcomes, mortality increased to only 2.2% compared with 9.8% in Gupta's study. Finally, while ICU LOS was slightly less at 36 h, hospital LOS was much longer at 8 days. There have been no other studies of large cohorts of ICU patients admitted with asthma from the USA in the last 2 decades.

Moghaddas et al. [7] reported on the high incidence of patients with drug abuse (26%) among asthma admissions to ICU between 2010 and 2014 in an Australian center. However, this study was small and occurred in an inner city hospital in Australia. This hospital treats a unique population with a high prevalence of drug abuse. Thus, the findings reported by these investigators are unlikely to apply to other settings.

### Implications of study findings

Our findings imply that both in the USA and ANZ, asthmatic patients make up a small proportion of ICU admissions and have a low mortality. Moreover, the ANZ findings imply that since 2003 there has been a

**Table 2.** Intubated patients with asthma: ANZICS vs. eICU cohorts.<sup>a</sup>

|                          | ANZICS (n = 544) | eICU (n = 186)   | P value |
|--------------------------|------------------|------------------|---------|
| Age (y)                  | 45 (32–57)       | 41 (30–52)       | 0.04    |
| Female                   | 339 (62.3%)      | 119 (64.0)       | 0.73    |
| BMI (kg/m <sup>2</sup> ) | 30.2 (24.4–36.0) | 28.3 (23.5–34.9) | 0.08    |
| Died ICU, n (%)          | 11 (2.0%)        | 1 (0.54%)        | 0.31    |
| Died hospital, n (%)     | 13 (2.4%)        | 2 (1.1%)         | 0.38    |
| ICU LOS (h)              | 75 (46–143)      | 61 (38–102)      | 0.08    |
| Hospital LOS (h)         | 154 (94–259)     | 114 (80–187)     | <0.001  |
| APACHE score             | 51 (38–68)       | 48.5 (40–60)     | 0.20    |
| FiO <sub>2</sub>         | 0.5 (0.35–0.7)   | 0.5 (0.4–0.6)    | 0.97    |
| PaO <sub>2</sub> (mmHg)  | 98 (74–145)      | 107 (82–164)     | 0.04    |
| pH                       | 7.26 (7.12–7.36) | 7.32 (7.26–7.40) | <0.001  |
| PaCO <sub>2</sub> (mmHg) | 54 (40–77)       | 46 (39–55)       | <0.001  |
| HR (beats/min)           | 121 (110–135)    | 126 (112–142)    | 0.02    |
| RR (breaths/min)         | 20 (10–32)       | 32 (14–41)       | <0.001  |
| MAP (mmHg)               | 70 (62–110)      | 65 (56–132)      | 0.50    |

Abbreviations: BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; LOS: length of stay.

<sup>a</sup>All continuous data is presented as medians with interquartile range.

**Table 3.** Cox proportional hazard model—whole cohort.

| HR for shorter ICU LOS  |             |           |           |         |
|-------------------------|-------------|-----------|-----------|---------|
|                         | Coefficient | HR        | HR 95% CI | P value |
| ANZICS APD              | –           | 1.0 (ref) | –         | –       |
| eICU CRD                | 0.21        | 1.24      | 1.13–1.35 | <0.001  |
| Age                     | –0.01       | 0.99      | 0.99–0.99 | <0.001  |
| APACHE score            | –0.01       | 0.99      | 0.98–0.99 | <0.001  |
| Female                  | –0.07       | 0.94      | 0.86–1.02 | 0.11    |
| Intubated               | –0.72       | 0.48      | 0.44–0.54 | <0.001  |
| HR shorter hospital LOS |             |           |           |         |
| ANZICS APD              | –           | 1.0 (ref) | –         | –       |
| eICU CRD                | 0.26        | 1.29      | 1.18–1.41 | <0.001  |
| Age                     | –0.01       | 0.98      | 0.98–0.99 | <0.001  |
| APACHE score            | –0.01       | 0.99      | 0.99–0.99 | <0.001  |
| Female                  | –0.12       | 0.88      | 0.81–0.96 | 0.003   |
| Intubated               | –0.40       | 0.67      | 0.60–0.74 | <0.001  |

Abbreviations: HR: hazard ratio; APACHE: Acute Physiology and Chronic Health Evaluation; LOS: length of stay.

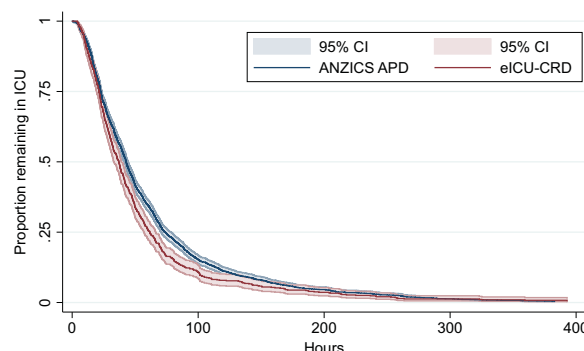
**Table 4.** Cox proportional hazard model—intubated cohort.

|                             | Coefficient | HR        | HR 95% CI | P value |
|-----------------------------|-------------|-----------|-----------|---------|
| HR for shorter ICU LOS      |             |           |           |         |
| ANZICS APD                  | –           | 1.0 (ref) | –         | –       |
| eICU CRD                    | 0.11        | 1.12      | 0.93–1.35 | 0.23    |
| Age                         | –0.00       | 1.00      | 0.99–1.00 | 0.91    |
| APACHE score                | –0.01       | 0.99      | 0.98–0.99 | <0.001  |
| Female                      | –0.002      | 1.00      | 0.85–1.17 | 0.98    |
| HR for shorter hospital LOS |             |           |           |         |
| ANZICS APD                  | –           | 1.0 (ref) | –         | –       |
| eICU CRD                    | 0.20        | 1.23      | 1.02–1.48 | 0.03    |
| Age                         | –0.01       | 0.99      | 0.99–0.99 | 0.009   |
| APACHE score                | –0.01       | 0.99      | 0.98–0.99 | <0.001  |
| Female                      | –0.07       | 0.93      | 0.79–1.09 | 0.35    |

Abbreviations: HR: hazard ratio; APACHE: Acute Physiology and Chronic Health Evaluation; LOS: length of stay.

decrease in hospital mortality and a marked decrease in the rate of invasive mechanical ventilation. In addition, they imply that both mortality and invasive ventilation rates are much less than reported in previous UK studies and establish an important performance benchmark for both at a global level.

Our findings imply that USA patients are more likely to be admitted to ICU with higher levels of illness

**Figure 3.** Kaplan–Meier plot of time to ICU discharge for the two study cohorts.

severity and yet remain under ICU and hospital care for a shorter period, suggesting either greater efficiency of care or greater pressure to avoid health care costs or both. Such findings provide an important efficiency benchmark for the care of such patients at a global level.

Moreover, the available physiological data in patients treated with invasive mechanical ventilation patients suggest a different approach to mechanical ventilation in ANZICS ICU compared with eICU USA centers with acceptance of a greater level of permissive hypercapnia, and the pursuit of lower PaO<sub>2</sub> targets in ANZ. Further investigations are needed to better understand the possible impact of this difference in practice.

Finally, our findings imply that even patients with a pre-ICU respiratory arrest have a low mortality and that female sex and age modulate the duration of ICU stay suggesting the need to persist with resuscitation efforts on all such patients.

### Study strengths and limitations

This is the first study to directly compare CAS outcome between two healthcare systems and the largest

study of CAS patients admitted to ICU in the literature. It involved two large patient cohorts with many relevant demographic and physiological characteristics included for comparison between the two groups, as well as data on invasive ventilation rates, mortality and duration of ICU and hospital care. The types of hospitals included a mix of tertiary and other hospitals increasing the external validity of the findings and the global relevance to high-income countries of their implications. Moreover, APACHE II has been specifically validated to assess disease severity in acute asthma [19]. The findings of similarities in some characteristics and outcomes, but also of significant differences in patterns of care, ventilation and ICU and hospital stay are clear and carry a high level of significance, making it unlikely that they represent a type I error and suggesting the need to explore underlying causes and possible improvements in efficiency.

There are potential limitations to our study. The ANZICS APD only records one primary APACHE diagnosis, and relying on this diagnosis may have introduced selection bias. Some patients included may have had an allergic or anaphylactic reaction without asthma, and those asthmatic patients who had a cardiac or respiratory arrest were not included in the study. The health insurance status of patients from the US was unavailable; this might affect access of patients to medical care, and therefore influence the nature of disease process. Data on NIV use were not available within the ANZICS APD and thus could not be compared. However, data on invasive ventilation was clear and consistent in both data sets. The ventilator settings during invasive mechanical ventilation were not available and can only be partly inferred from the physiological characteristics. However, the differences in respiratory rate in such patients were striking, making it very likely that they reflected such settings. We only have hospital outcomes and cannot comment on, pre-ICU treatment, readmissions or long-term management. However, no study has yet been able to assess such complex aspects of pre and post ICU care. This is an inherent limitation of all large database studies. Our explanations for the differences between the two cohorts in terms of physiology, treatment and outcome remain speculative. However, they have public health implications with regard to cost and efficiency of care. Finally, it was not possible to test the hypothesis that changes in community-based care might be a major reason for changes in the incidence of severe asthma, as pre-admission data were not available. However, in the absence of any other logical explanation, it seems reasonable to

suggest that such changes might have contributed to our finding that, over the past decade, there have been reductions in the rate of asthma admission and intubation in ANZ ICUs.

## Conclusions

The characteristics and outcomes of patients admitted to ANZ and USA ICUs with asthma were similar and their invasive ventilation rate was low and the mortality was very low. However, asthmatic patients made up a greater proportion of ICU patients in ANZ ICUs while USA patients appeared more acutely ill. Moreover, mechanically ventilated patients in ANZ ICUs appeared to be treated to different lower respiratory rates, more hypercapnia and lower O<sub>2</sub> targets. In association with such management, patients admitted to Australia and New Zealand study ICUs had longer ICU and hospital stays. These findings have public health implications in relation to ICU admission rates due to CAS and provide important epidemiologic information for comparisons with other health care systems. They also provide baseline data for comparisons of changes in care and outcome over time, and set a benchmark for invasive ventilation rates, survival rate, and duration of ICU and hospital stay, against which institutions or other health care systems can measure their performance and efficiency.

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