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Outcome of oncology patients in the pediatric intensive care unit

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Abstract. We evaluated the outcome of oncology patients in the Pediatric Intensive Care Unit (PICU) from a total of 72 consecutive admissions. Severity of illness and quantity of care were measured by the Physiologic Stability Index (PSI) and the Therapeutic Intervention Scoring System (TISS), respectively. The overall mortality was 51% and was especially high in patients admitted for acute organ system failure (OSF) – 66%. Acute respiratory failure was the most frequent OSF (73%) and the most common cause for PICU admission. A poor outcome was associated with severe leucopenia (<1000 WBC/mm^3, 91% mortality), acute renal failure (94% mortality) and central nervous system deterioration (83% mortality). When the outcome was predicted using a quantitative algorithm the observed mortality was significantly higher than the predicted for all admissions with a PSI higher than 5. Improved scoring systems are required to enable characterization of pediatric cancer patients admitted to the PICU.

Key words: Children – Cancer – Prognosis – Intensive care

The outcome of adult oncology patients admitted to the Intensive Care Unit (ICU) has been shown to be poor despite increasing therapy [1–3]. Nevertheless, a disproportionate amount of resources were employed on this poor outcome group. The nature, spectrum of diseases, course and prognosis of childhood malignancies are different from that seen in adult cancer. Thus, physicians caring for acutely ill pediatric cancer patients cannot rely on information from and experience with adults [4]. There has been only one study addressing itself to this issue [5]. This was a retrospective hospital chart review of patients including only one major subgroup of the pediatric cancer population: children with hematologic malignancy.

The purpose of the present study was to evaluate, prospectively, the outcome of pediatric patients with underlying malignancies admitted to the PICU, to delineate factors that may affect the prognosis, and to assess the applicability of physiologic-based scoring methods and prognostic predictors in this unique group of patients.

Patients and methods

This prospective study is the result of collaboration between two multidisciplinary PICUs following the same study protocol: the Beilinson Medical Center, Petah-Tikva, Israel (Hospital A) and Childrens Hospital, Los Angeles, USA (Hospital B). Both medical centers are tertiary centers for pediatric intensive care and pediatric oncology. Patients were admitted at the request of the Pediatric Oncology service, on the understanding that once the acute illness had been overcome, further therapy would be provided for the basic disease from which a successful outcome was still possible.

Patients with newly diagnosed brain tumors who were admitted to the PICU for short-term post-operative observation following ventriculo-peritoneal shunt operation were not included in this study. These patients were not subjected to oncologic therapy at that time and did not have organ system failure. Patients with brain tumors who were admitted because of acute deterioration (sepsis, acute respiratory failure, etc.) or for post-operative care and procedures while they were under oncologic follow-up or treatment, were included in the study.

Data were collected daily from 72 consecutive admissions (47 in Hospital A and 25 in Hospital B) of pediatric cancer patients to the PICUs between 1986 and 1988. The information included: 1) demographic data, 2) past-medical history, 3) specific cause for PICU admission, 4) type of PICU admission criteria (acute organ system deterioration versus procedure and postoperative observation), 5) number and specific types of organ system failure (OSF), 6) length of PICU stay, 7) severity of illness, and 8) amount and type of treatment each patient received in the PICU. Organ system failure was defined using the criteria and principles of Wilkinson et al. [6]. These principles are based on clinical and laboratory measurements and the nature of supportive care. OSFs were diagnosed as extreme physiologic abnormalities, extremely abnormal laboratory values, or the need to use a life-sustaining therapy in order to ameliorate or eliminate these physiologic or laboratory abnormalities [6]. The variables were evaluated and correlated to outcome. Non-survival was defined as death in the PICU. Whenever a "do not resuscitate" order was applied, it was on the basis of the current disease status regardless of baseline oncologic disease. These patients died in the PICU ("non-survivors").

Two scoring systems applicable to pediatric intensive care were used. Between them they provide objective measures for determining severity

Table 1. Mortality by underlying disease

Underlying disease	No.	Died (%)
Hematologic malignancies:		
Acute lymphoblastic leukemia	15	5 (33)
Acute myeloblastic leukemia	10	8 (80)
Chronic myelocytic leukemia	4	2 (50)
Congenital mixed leukemia	1	0
Acute nonlymphocytic leukemia	2	2 (100)
Hodgkin lymphoma	3	2 (67)
Non-Hodgkin lymphoma	4	2 (50)
Histiocytosis	4	3 (75)
Subtotal	43	24 (56)
Solid tumors:		
Neuroblastoma	9	7 (78)
Rhabdomyosarcoma	5	2 (40)
Ewing sarcoma	2	1 (50)
Osteogenic sarcoma	1	0
Meningosarcoma	1	0
Wilms tumor	4	0
Astrocytoma	1	1 (100)
Adrenal cortex carcinoma	1	0
Hepatoblastoma	2	1 (50)
Lung tumor	1	0
Primitive neuroectodermal tumor	1	1 (100)
Ependymoma	1	0
Subtotal	29	13 (45)
Total	72	37 (51)

of illness, prediction of outcome, cost and manpower needs and enable comparison of patient care between PICUs [7–11].

1. The Therapeutic Intervention Scoring System (TISS) was used daily to quantitate therapy and resources expended by assigning points from 1–4 to various therapeutic interventions based on complexity and invasiveness [7, 9]. The TISS is applicable to children in PICU [7] and to acutely ill cancer patients [12]. The higher the score, the more care provided.

2. The Physiologic Stability Index (PSI) was used daily to assess objectively the severity of illness by quantitation of the degree of abnormality in 34 variables from 7 physiologic systems. This scoring system was designed specifically for the PICU population [8]. The higher the score, the more physiologically unstable the patient. Scores less than 9 generally correspond to low mortality risk, while scores greater than 24 correspond to high mortality risk [8, 13, 14].

The probability of death was calculated using the algorithm formulated by Pollack et al. [14]. This algorithm predicts the outcome of patients in the PICU according to a weighted sum of admission PSIs for the various organ systems and age. This mortality predictor has been assessed in 9 PICUs and was found to be highly reliable [14]. In addition, the relationship between the admission-day PSI and patient age and the probability of death was characterized by a multivariate logistic regression. We used the equation for logistic function derived by Pollack et al. [14] and compared the weightings assigned to each organ system with those of Pollack et al.

Statistical evaluation of the data and comparison with published mortality prediction algorithms were done using SAS (SAS Institute, Cary, NC). Since most of the data collected were of the non-continuous interval type (i.e. yes or no, or points), non-parametric as well as parametric analyses were used. Methods used included: Student t test, the Wilcoxon Rank Sums test for comparison of unpaired data, Wilcoxon Signed Ranks test for comparison of paired data, Fisher's Exact test, χ^2 test and Kruskal-Wallis test for comparison of multiple data. Whenever the distribution of a non-parametric variable was not a Gaussian distribution a transformation using square root was used and the Student t test was then applied. A $p \leq 0.05$ was taken to be significant.

Results

The patient population, underlying disease and global outcome are shown in Table 1. The ratio of admissions for acute organ system deterioration to admissions for procedures, the age range (Hospital A: 5.5 ± 4.0 years, range 0.04–18; Hospital B: 8.8 ± 5.3 years, range 0.5–19), the length of PICU stay for survivors and non-survivors and the overall mortality rate (53% for Hospital A and 48% for Hospital B) were comparable ($p > 0.05$; Student-t-test and Wilcoxon Rank Sum). Similarly, the severity of illness evaluated by admission, maximal and average PSI scores and the amount of therapy assessed by admission, maximal and average TISS scores were not different between the two hospitals ($p > 0.05$; Student-t-test and Wilcoxon Rank Sum), so the results were combined (Table 2).

The survival rate did not correlate with sex, age nor duration of stay in the PICU (Wilcoxon Rank Sum). The most common cause for PICU admission was acute respiratory failure – 27 patients (37%), with a mortality rate of 74%. All of them required intubation and ventilatory support. Acute parenchymal lung disease occurred in 23/27 including: pneumonia, adult respiratory distress syndrome – non cardiogenic pulmonary edema and pulmonary bleeding. Four patients had acute obstructive airway disease: upper airway obstruction, vocal cord paralysis and right main bronchus obstruction. Out of these 4 patients 3 died. Cardiovascular failure was the main cause of PICU admission in 17 cases (24%) with a mortality of 47%. Eleven (15%) patients were admitted with the predominant problem of central nervous system (CNS) deterioration; this group had the highest mortality rate – 90%. The overall mortality was 51%, but of 16 (22%) patients admitted for medical or surgical procedures including post-operative care, none died ($p < 0.0001$, Fisher's Exact test). The specific causes of PICU admission for these patients were: major surgery for tumor resection, limb amputation, open lung biopsy and exchange transfusion. Excluding this subgroup, the overall mortality was 66% (37/56).

Mortality correlated with the number of OSFs per patient: 0%, 43%, 64%, 81% and 100% mortality for 1, 2, 3, 4, and 5 OSFs, respectively ($p < 0.0001$, χ^2). However, most patients had only 1–3 OSFs on admission, and those who did not survive developed further OSFs later in the course of their PICU stay. Some OSFs were associated with a higher mortality. For example, patients with renal failure (oliguric in all cases) had 94% mortality (15/16); none of these presented with renal failure on admission, but developed it later in addition to 2–4 other OSFs. Patients with CNS deterioration (coma, encephalopathy, seizures) due to tumor invasion, intracranial bleeding or CNS infection had a mortality of 83% (20/24). In 45% of them (9/20), CNS deterioration was also the main cause of admission. This high mortality was not related to the number of OSF (χ^2, Table 3).

Forty-six patients (64%) had a leucopenia of less than 3000 WBC/mm^3. In 18, whose white count was never less than 1000 WBC/mm^3, the mortality was 61% (11/18), while in 22 patients whose white cell count per-

Table 2. Severity of illness (PSI) and amount of therapy (TISS) in both hospitals (Adm. = admission, Max. = maximal, Average = average per day, LOS = length of stay in days). Values as mean; range. There was no significant difference between the two hospitals

Hospital	PSI			TISS			LOS
	Adm.	Max.	Average	Adm.	Max.	Average	
A (total)	11.3; 4–31	13.8; 4–41	11.2; 3–30	36.2; 5–69	45.7; 11–70	38.1; 7–69	7.9; 1–51
Survived	6.4; 4–14	8.1; 4–24	6 ; 3–15	29.1; 5–53	39.2; 11–70	28.8; 7–46	7.8; 1–51
Died	15.7; 8–31	18.9; 12–41	15.7; 11–30	42.5; 20–69	51.4; 36–69	46.3; 28–69	7.9; 1–31
B (total)	11.6; 1–31	13.9; 2–31	10.9; 2–31	38.8; 13–75	46.6; 15–75	38.5; 14–75	9.6; 1–46
Survived	7.8; 1–16	9.3; 2–16	5.8; 2–9	34.2; 13–59	34.2; 15–73	31.2; 14–46	9.5; 2–46
Died	14.8; 6–31	18.8; 7–31	16.5; 9–31	43.1; 24–75	50.9; 25–75	46.5; 25–75	9.7; 1–22
A+B	11.4; 1–31	13.8; 2–41	11.5; 2–31	37.6; 5–75	46.0; 11–75	38.0; 7–75	8.5; 1–51
Survived	6.9; 1–16	8.3; 2–24	5.9; 2–15	31.9; 5–59	40.5; 11–73	29.1; 7–46	8.4; 1–51
Died	15.4; 6–31	18.9; 7–41	15.9; 9–31	43.0; 20–75	51.2; 25–75	46.4; 25–75	8.5; 1–31

Table 3. Effect of central nervous system deterioration on mortality at different amounts of organ system failure

No. of OSF	Patients with CNS involvement	Died	Mortality (%)
2	6	5	83
3	3	2	67
4	10	8	80
5	5	5	100

Table 4. Multivariate analysis of organ-system subscores on the PSI

System	Weighting	SEM	T value	PSI score mean ± SD
Cardiovascular	0.496	0.193	2.56	1.83 ± 2.08
Respiratory	0.454	0.239	1.90	2.97 ± 2.21
Renal	−0.117	1.031	−0.11	0.24 ± 0.70
Neurologic	0.888	0.258	3.44	1.24 ± 2.27
Hematologic	0.330	0.177	1.87	3.71 ± 2.67
Gastrointestinal	1.060	0.926	2.22	0.48 ± 0.94
Metabolic	0.059	0.289	−0.20	1.12 ± 1.24
Age	0.002	0.001	0.26	78.37 ± 55.65
Constant	−4.740	1.29	−3.66	

sistently remained under 1000 WBC/mm^3 (severe leucopenia), the mortality was 91% (20/22; $p < 0.0001$, Kruskal-Wallis test), regardless of the number of OSF (Fisher's exact test, $p = 0.031$). The 6 remaining patients had initial counts of less than 1000 WBC/mm^3 (severe leucopenia) which subsequently returned to normal; all of these patients survived.

Twenty-nine patients had sepsis with positive blood cultures. Of these, 23 died (80%) versus 14 deaths out of 43 patients without sepsis (33%). Of the 23 septic patients who did not survive, 16 had < 1000 WBC/mm^3, 5 patients had 1000–3000 WBC/mm^3, and only 2 had normal WBC count. Six patients with sepsis survived: one had < 1000 WBC/mm^3, 3 patients had 1000–3000 WBC/mm^3 and 2 had normal WBC count.

Patients who died in the PICU received a higher amount of therapy than those who survived (Table 2). Admission TISS scores as well as maximal and average TISS scores were higher in non-survivors ($p < 0.01$, Wilcoxon Rank Sum). Similarly, patients who died had significantly higher average PSIs as well as higher maximal and admission PSIs ($p < 0.01$, Wilcoxon Rank Sum). Nevertheless, there was a significant overlap between the two groups, especially for the day of admission. Five patients who survived (15%) had an admission PSI score in the range of 14–16 points while 25 children who did not survive had a PSI score ≤ 17 for the day of admission.

When the patients were grouped according to PSI on admission (Fig. 1), and the observed outcome was compared to the predicted for each group according to the algorithm of Pollack et al. [14]. It was found that there was a significantly higher observed mortality for all PSI groups except the 0–5 group (Fig. 1, categories A and C). The predicted mortality based on our data (Fig. 1, catagory B) was obtained by applying the weighting derived from the multivariate analysis of our data (Table 4) to Pollack's equation. Hence categories B and C of Fig. 1 are very close and do not differ significantly. The multivariate analysis of organ system subscores on the PSI and age showed that weighting was different from that previously reported by Pollack et al. [14]. The neurologic system had the highest weighting followed by the cardiovascular, respiratory and hematologic systems (Table 4).

Discussion

Children with underlying malignancy who require intensive care are a unique group with respect to the amount of therapy applied and survival rate. Much of our present knowledge of cancer patients with multiple OSF comes from adult ICU populations where there is a mortality of 24–90% – a much higher rate than that of concurrently admitted patients without cancer [12, 15–17]. This information, however, is not applicable to children because of the difference in clinical spectrum of disease, patient

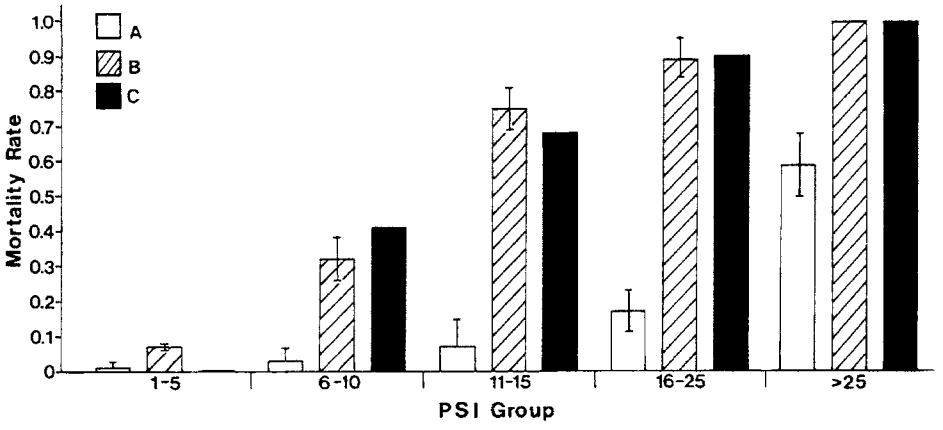

Fig. 1. Histogram of the predicted mortality probability according to Pollack et al. [14] (A) and our data (B) and the observed mortality (C) for pediatric oncology patients admitted to the intensive care unit. The data are presented as means ± S.E. and are grouped into 5 PSI intervals according to Pollack et al.

characterization and the prognosis of the underlying disorder. One recently published paper [5] presents combined data from 3 PICUs (2 in Australia and 1 in Canada) concerning the short-term outcome of children with hematologic malignancy only. This was, however, a retrospective study based on chart reviews, and hence the degree of physiologic abnormality and care were not quantified.

In the present study, we combined data from 2 PICUs. This is justified based not only on similarities in management, patient population and overall outcome, but also on similarities in objective measurements of severity of disease (PSI) and amount of therapy (TISS). One of the advantages of using these scoring systems is that they objectively evaluate the degree of physiologic abnormality and the amount of therapy and can be used to calculate the probability of death for the group regardless of the patients' diseases, diagnoses or previous treatments for underlying illnesses [8, 14]. They are especially useful in descriptive studies [14]. The TISS, which has been found applicable to children and to acutely ill cancer patients, is associated with severity of illness, outcome and cost, and also enables quantitative comparison of patient care [2, 7, 9, 12, 13, 18]. Nevertheless, because the TISS may measure aggressiveness of therapy rather than the indications for it, we also used the PSI scoring system which is based on clinical condition and physiologic variables. The PSI, which has been developed specifically for pediatric ICUs, has only recently been validated in 9 institutions and showed accurate mortality prediction [14].

The mortality of pediatric oncology patients in the present series was unexpectedly high – 51% – compared to overall general mortality of 7.2% and 8.9% in the two PICUs (Hospitals A and B, respectively; mortality = 5.7% and 7.1% when cancer patients were excluded) which is within the reported range of 3–17.6% in 9 other PICUs [14]. One may argue that the significantly higher mortality compared to the predicted rate may result from a low quality of medical care in both PICUs. Although we do not have a control group of non-cancer patients in these PICUs, the fact that the overall mortality in both multidisciplinary PICUs is not different from the reported rate argues against this. Moreover, two thirds of the patients in our series who were admitted for acute organ system deterioration died in the ICU. This rate is very similar to the findings in the retrospective study [5] in which the overall mortality was 48%, and as high as 60% for children with hematologic malignancy who were admitted for acute deterioration; 7% of the patients who were admitted for post-operative care in that series did not survive versus 100% survival in the present report. Our results are also not very different from those in adult cancer patients where the mortality of patients admitted for acute OSF was as high as 90% [12, 15–17].

Comparing the present series to other pediatric (non-cancer) intensive care groups [7, 13, 14, 18], the mortality in our series was higher. The mean PSI and TISS scores for survivors in those reports was higher which means that more patients with relatively low TISS and PSI scores in our study died. When the algorithm for predicting mortality based on admission PSI scores and age [14] was applied to the present series of patients, a significantly large discrepancy between observed and predicted mortality was noted. Although for PSIs of 5 or less, the observed mortality was lower than predicted, patients with PSIs higher than 5 had a much higher observed mortality. Thus, the equation of the probability of death when utilized for pediatric oncology patients in the PICU requires different and higher weights of organ-system subscores than those previously suggested for the general PICU population.

Compared to the retrospective study of Butt and associates [5], our results show that involvement of the brain by the underlying oncologic disease, with deterioration of consciousness or seizures, implies a very poor prognosis. Butt et al. also found such a high mortality (>70%) when the encephalopathy was secondary to either sepsis or intracranial bleeding but noted a lower mortality rate when CNS deterioration was due to leukemic infiltration, chemotherapy or metabolic acidosis. The ominous nature of the development of acute renal failure has been documented in this study, and also in other pediatric and adult ICU populations [18–20].

In non-cancer patients, the number of failed organ systems has been proposed as significantly associated with mortality in pediatric ICU. This was not, however, sufficiently discriminating to determine withdrawal of support; further, all OSF *except hematologic failure* significantly decreased the probability of survival [6]. Our results show that in pediatric cancer patients, bone mar-

row failure and especially its severity, are major factors affecting mortality. This again highlights the unique nature of the pediatric cancer group. It should be noted that the PSI scoring system does not separate between leucopenia (less than 3000 cells/mm^3) and severe leucopenia (less than 1000 cells/mm^3, or severe neutropenia i.e. less than 500 neutrophils/mm^3). Nevertheless, in our series this does seem to affect outcome.

Comparable to the results of Butt et al. [5], the mortality of patients with sepsis was higher than of patients without positive blood cultures (80% versus 33%). This implies that the prognosis of oncology children with sepsis admitted to the PICU is poor. However, these patients already had organ system failure and the fact that 20% of them still survived the combination of sepsis, severe leucopenia and organ system failure may be encouraging.

We conclude that the mortality of pediatric oncology patients requiring intensive care is unexpectedly high when assessed against the rate predicted by existing objective methods. These general scoring methods cannot be applied to this population without considering the nature and severity of the underlying disease and the magnitude of bone marrow failure. Because bone marrow failure is such a severe complication, it might be appropriate to admit some of pediatric cancer patients with this complication earlier to the PICU before other organs have failed.

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References

1. Civetta JM (1973) The inverse relationship between cost and survival. J Surg Res 14:265–269
2. Cullen DJ, Ferrara LC, Briggs BA, Walker PF, Gilbert J (1976) Survival, hospitalization charges and follow-up results in critically ill patients. N Engl J Med 294:982–987
3. Turnball AD, Carlon G, Baron R, Sichel W, Young C, Howland W (1979) The inverse relationship between cost and survival in the critically ill cancer patient. Crit Care Med 7:20–22
4. Turnball AD, Goliner PL, Silverman DG, Howland W (1975) The role of an intensive care unit in a cancer center: an analysis of 1,035 critically ill patients treated for lifethreatening complications. Cancer 37:82–84
5. Butt W, Barker G, Walker G, Gillis J, Kilham H, Stevens M (1988) Outcome of children with hematologic malignancy who are admitted to an intensive care unit. Crit Care Med 16:761–764
6. Wilkinson D, Pollack MM, Ruttimann UE, Glass NL, Yeh TS (1986) Outcome of pediatric patients with multiple organ system failure. Crit Care Med 14:271–274
7. Yeh TS, Pollack MM, Holbrook PR, Fields AI, Ruttimann UE (1982) Assessment of pediatric intensive care – application of the therapeutic intervention scoring system. Crit Care Med 10:492–500
8. Yeh TS, Pollack MM, Ruttimann UE, Holbrook PR, Fields AI (1984) Validation of a physiologic stability index for use in critically ill infants and children. Pediatr Res 18:445–451
9. Cullen DJ, Civetta JM, Briggs BA, Ferrara LC (1975) Therapeutic intervention scoring system: a method of quantitative comparison of patient care. Crit Care Med 2:57–60
10. Pollack MM, Ruttimann UE, Glass NL, Yeh TS (1985) Monitoring patients in pediatric intensive care. Pediatrics 76:719–724
11. Glass NL, Pollack MM, Ruttimann UE (1986) Pediatric intensive care: who, why and how much? Crit Care Med 14:222–226
12. Silverman DG, Golinder PL, Kaye BA, Howland WS, Turnball AD (1975) The therapeutic intervention scoring system. An application to acutely ill cancer patients. Crit Care Med 3:222–225
13. Pollack MM, Yeh TS, Ruttimann UE, Holbrook PR, Fields AI (1984) Evaluation of pediatric intensive care. Crit Care Med 12:376–383
14. Pollack MM, Ruttimann UE, Getson PR (1987) Accurate prediction of the outcome of pediatric intensive care. A new quantitative method. N Engl J Med 316:134–139
15. Carlon GC (1988) Admitting cancer patients to the intensive care unit. Crit Care Clin 4:183–193
16. Hauser MJ, Tabak J, Baier H (1982) Survival of patients with cancer in a medical critical care unit. Arch Intern Med 142:527–529
17. Schuster DP, Marion JM (1983) Precedent for meaningful recovery during treatment in a medical intensive care unit. Outcome in patients with hematologic malignancy. Am J Med 75:402–408
18. Rothstein P, Johnson P (1982) Pediatric intensive care: factors that influence outcome. Crit Care Med 10:34–37
19. Casali R, Simmons RL, Najarian JS, Von Hartizsch B, Buselmeier TJ, Kjelstrand CM (1975) Acute renal insufficiency complicating major cardiovascular surgery. Ann Surg 181:370–375
20. Scott RB, Cameron JS, Ogg CS, Bewick M (1972) Why the persistently high mortality in acute renal failure? Lancet II:75–78

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