

# FACTOR INFLUENCING CASE-FATALITY RATE OF SEPTICEMIC CHILDREN

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**Abstract.** One hundred and forty episodes of septicemic children seen at Songklanagarind Hospital during a period of two years were reviewed to determine factors related to mortality. One hundred episodes (70.4%) of septicemia were hospital-acquired in which 98 (69%) were caused by gram negative bacilli, with *Pseudomonas* being the most common agent. Thirty episodes were from gram-positive cocci and eight were from polymicrobial infections. The remainder were caused by *Candida* species.

The overall case-fatality rate was 28.6%. Using a logistic regression model, appropriateness of antibiotic use and host status (being newborn or a compromised host compared to a normal host), but not neutropenia and acquisition of infection were the only statistically significant risk factors. The exact odds ratio of inappropriate use of antibiotic adjusted for host status was 13.6 (95% confidence limits = 5.7- 32.3). Percentages of inappropriate usage among the premature and full term newborn, compromised host and normal were 50, 11, 28 and 24, respectively.

Inappropriate antibiotic use was the major cause of case-fatality in the study population. It was more common among the premature newborn and compromised hosts.

## INTRODUCTION

The importance of septicemia as a major cause of morbidity and mortality in pediatric patients is well recognized (Winchester *et al*, 1977; Bryan *et al*, 1984). Antimicrobial therapy remains the mainstay of treatment (Kreger *et al*, 1980; Bryan *et al*, 1983) but many other factors also account for determining the outcome such as severity of underlying disease (Winchester *et al*, 1977; Bryan *et al*, 1984; Kreger *et al*, 1980; McCue, 1985; Scheckler, 1977) neutropenia (Kreger *et al*, 1980; Bonadio *et al*, 1991) and hospital acquired infection. (Kreger *et al*, 1980). To define the importance of the factors influencing the fatality rate of septicemia we conducted a retrospective review of all episodes of septicemia documented in pediatric patients at Songklanagarind Hospital, a 700 bed teaching hospital in Southern Thailand, during a 2-year period. The data were subsequently analysed using multiple logistic regression analysis to identify significant risk factors for septicemic mortality.

## MATERIALS AND METHODS

Records from the Microbiology Laboratory were reviewed for all isolates of microorganisms from patient blood culture specimens obtained during the period January 1, 1985, through December 31, 1986. Hospital records of all patients were then reviewed in detail. Episodes of septicemia were defined on the basis of isolation from blood cultures on microorganisms usually considered to be pathogens (Brenner and Bryan, 1981). Only patients whose clinical features were consistent with septicemia were included for study. Microorganisms frequently regarded as contaminants of blood culture, such as *Staphylococcus epidermidis*, were included only if isolated from multiple blood cultures and the isolates were given clinical significance by the attending physicians, as documented in the medical records. Postmortem blood culture specimens were excluded.

Septicemias were considered to be hospital ac-

quired if the first positive blood cultures were obtained on or after the third day of hospitalization. (McGowan *et al*, 1975). Septicemias occurring before this time were considered community acquired unless the bacteremia was clearly related to a procedure which was performed after hospital admission (Brenner and Bryan, 1981). Septicemias occurring in newborn infants, either intrapartum acquisition or the result of hospitalization, were also considered to be hospital acquired infections (Allen and Oliver, 1979). Aerobic blood cultures were obtained and processed by conventional techniques using standard media, which generally consisted of brain heart infusion broth and subculture in chocolate agar. Quantitative blood cultures were not performed.

Antimicrobial therapy was considered to be appropriate if: (1) the antimicrobial agent or components of the combination of antimicrobial agents were effective *in vitro* against the pathogen isolated, (2) considered to be a drug of choice (Nelson, 1985), and/or (3) was administered in an effective dose and by an acceptable route of administration within 48 hours after the first positive blood culture was obtained from the patient.

Patients were classified into three categories based on their immunologic condition: (1) newborn infant; (2) patient with underlying immunocompromised condition, either directly from the underlying disease or the effect of an immunosuppressive drug used for treating the disease (Joshi and Schimpff, 1985); (3) normal host.

Statistical analysis was carried out by Chi-square test or Fisher's exact probability test. Crude odds ratios and their 95% confidence intervals were computed for factors influencing the fatality rate. Logistic regression was used to obtain estimates of risk and statistical tests of significance after simultaneously controlling the other variables.

## RESULTS

One hundred forty-four episodes of septicemia were reviewed in 133 patients; 7 patients had two episodes of septicemia and 4 episodes were excluded from further analysis because of being postmortem specimens. Fifty-five cases were newborn infants (28 cases term infants and 27 premature infants), 35 cases were patients with an underlying immunocompromised condition, (20 acute leukemia, 3

lymphoma, 7 other malignancy, 2 severe aplastic anemia, 2 severe malnutrition and 1 severe cirrhosis). Fifty cases were classified as normal immune hosts including 8 cases of rheumatic heart disease, 2 cases of thalassemia, 1 case of systemic lupus erythematosus (SLE), 1 case of idiopathic thrombocytopenic purpura (ITP) and 1 case of 25% body surface area second degree burn. The male to female ratio was 1.7 : 1.

Ninety-six episodes (68.6%) were caused by gram negative bacilli. The microorganisms isolated according to acquisition of infection, underlying condition and case fatality rate are shown in Table 1.

The overall case fatality rate was 28.6%. Case-fatality rates of gram negative, gram positive, *Candida* and polymicrobial septicemias were 29.2%, 23.3%, 50% and 25% respectively. The case-fatality rate from these four pathogen groups were not significantly different.

The crude odds ratios for various risk factors are shown in Table 2. Appropriateness of antibiotic usage was the strongest determinant of patient survival, followed by underlying host status, absolute neutrophil count and acquisition of infection.

The last column of Table 2 shows adjusted odds ratios obtained from the logistic regression model. Only the first two variables were statistically significant risk factors. The odds ratio of appropriateness of antibiotic use was still high (16.5) after being adjusted for host factors. In contrast to crude odds ratios which suggest the premature newborn was at highest risk and the full-term newborn was at lowest risk, logistic regression revealed that after adjusted for appropriateness of antibiotic use, the immunocompromised host was at the highest risk followed by full term and premature newborns, respectively. The odds ratios of the two groups of newborns were not significantly different. The discrepancy between crude odds ratios and those from logistic regression was due to the inappropriate antibiotic use (50%) in premature infants and relatively appropriate antibiotic treatment (89%) among the full term newborns, as shown in the lower part of Table 3.

Subsequent analysis by stratified exact method to obtain more accurate odds ratio provided the results shown in Table 4. By this method, the adjusted odds ratio of inappropriate use of antibiotic was a little lower than the crude odds ratio. The result of heterogeneity test of odds ratio was not statistically significant indicating that the variation of odds ratio among different host groups was due to chance.

Table 1

Microorganism isolated from 140 episodes of septicemia according to acquisition of infection, underlying condition and case fatality rate.

Microorganism (N)	Acquisition		Underlying conditions			Case-fatality rate (%)	
	Community	Hospital	Immunocompromised	Newborn	Normal		
<i>Pseudomonas</i> spp. (43)	4	39	7	27	9	30	
<i>Klebsiella pneumoniae</i> (11)	2	9	3	3	5	27	
<i>Enterobacter</i> spp. (9)	2	7	4	4	1	22	
<i>Escherichia coli</i> (8)	1	7	4	1	3	63	
<i>Salmonella</i> spp. (7)	5	2	2	0	5	0	
<i>Acinetobacter</i> spp. (5)	1	4	1	2	2	40	
<i>Serratia marcescens</i> (1)	0	1	0	0	1	0	
<i>Hemophilus parainfluenza</i> (1)	1	0	0	0	1	0	
Other aerobic Gram-negative bacteria (11) g	5	6	3	5	3	27	
<i>Streptococcus</i> spp. (15)	11	4	4	1	10	33	
<i>Staphylococcus</i> spp. (15)	8	7	2	6	7	13	
<i>Candida</i> spp. (6)	0	6	1	4	1	50	
Polymicrobial (8)	1	7	4	2	2	25	
Total	140	41	99	35	55	50	28.6

## DISCUSSION

In the present study the most important factor causing septicemic mortality was inappropriate antimicrobial therapy, especially in the patients classified as "normal host". The importance of antimicrobial therapy has been studied by Kreger *et al* (1980) which illustrates that appropriate antibiotic treatment reduced the fatality rate of those with bacteremia by approximately one-half among patients in each category of severity of underlying host disease, and in the studies summarized by Bryan *et al* (1983) that tend to show an improvement in survival when appropriate antibiotics are used. These results may conflict with other studies (Bryan *et al*, 1984; McCue, 1985) which did not show a significant improvement in mortality with the prompt use of antibiotics within 24 hours of the first positive blood culture obtained, with *in vitro* activity against the causative bacteria. Bryan *et al* (1984) did not exclude pseudobacteremia or contamination of cultures.

The benefit from the use of multiple antibiotics

with *in vitro* activity against the causative organisms was not studied here but was consistent with large studies showing no improvement in mortality with the use of combinations of antibiotics (Kreger *et al*, 1980; McCue, 1985). On the other hand, combination of an aminoglycoside and an antipseudomonal beta-lactam agent has improved survival in normal and neutropenic patients infected with *P. aeruginosa* (Hilf *et al*, 1989; The EORTC, 1987). Adequate empiric coverage for all likely pathogens may still require antibiotic combinations, especially for hospital-acquired infections.

Prompt and proper antibiotic treatment may prevent shock (Kreger *et al*, 1980) and other complications of bacteremia, the severity of the patients underlying illness, supportive medical care and the reversal of complications or causative problems eg neutropenia and visceral obstruction, which may have as great an effect on gram-negative bacteremia as the use of an appropriate empiric antibiotic regimen.

The fact that the premature newborns had the

Table 2

Case-fatality rate by different risk factors.

Factor	Case-fatality rate (%)	Crude odds ratio	*Adjusted odds ratio (95% c.i.)
<b>Appropriateness of antibiotic</b>			
Appropriate	14/101(14)	1	
Inappropriate	26/39(67)	15.8**	16.5(5.8-47.0)
<b>Host status***</b>			
Normal	6/50(12)	1	
Premature newborn	13/28(46)	6.4	5.2(1.4-19.8)
Full-term newborn	7/27(26)	2.6	6.3(1.4-27.5)
Immunocompromised	14/35(40)	4.9	7.8(2.0-29.7)
<b>Absolute neutrophil count</b>			
= > 1,000/mm <sup>3</sup>	26/100(24)	1	
< 1,000/mm <sup>3</sup>	12/25(48)	3.0***	—
<b>Acquisition</b>			
Community	7/41(17)	1	
Hospital	33/99(33)	2.4	—
<b>Sex</b>			
Male	21/88(24)	1	
Female	19/52(37)	1.84	—

\* by multiple logistic regression analysis

\*\* p < 0.001

\*\*\* p < 0.05

Table 3

Proportion of appropriate antibiotic usage among different groups of patients.

Classification	Appropriate/total	(per cent)	Chi square	p-value
<b>Sex</b>			0.19	0.66
Male	65/88	(74)		
Female	36/52	(69)		
<b>Acquisition</b>			1.39	0.24
Hospital acquired	68/99	(69)		
Community acquired	33/41	(80)		
<b>Host status</b>			9.03	0.028
Premature newborn	14/28	(50)		
Full - term newborn	24/27	(89)		
Immunodeficiency	25/35	(71)		
Normal	38/50	(76)		

Table 4

Case fatality rate by appropriateness of antibiotic stratified by underlying condition.

Host status	Case fatality rate appropriateness of antibiotic choice		*Odds ratio (95% CI) of inappropriate antibiotic
	appropriate	inappropriate	
Normal	0/36	6/12	inf (5.4-inf)
Full-term	4/24	3/3	inf (1.4-inf)
Premature	4/14	9/14	4.5 (0.7-30.0)
Immunodeficiency	6/25	8/10	12.7 (1.7-141.2)
Total	14/101	26/39	13.6 (5.7-32.3)**

\* all calculations in this table used exact statistical method

\*\* adjusted for host condition

lowest percentage of use of appropriate antibiotics may be explained by acquisition of nosocomial infection which usually resulted in infection with multi-resistant organisms. A relatively high percentage of inappropriate use of antibiotics among this group indicates a need to improve diagnostic procedures and management strategies for these patients.

The influence of the underlying condition of the host was also clearly in this analysis as shown in other studies (Kreger *et al*, 1980; McCue, 1985). High case-fatality rates in newborn infants with septicemia was also well recognized in the study conducted by Bryan *et al* (1984).

The higher mortality in neutropenic patients and hospital acquired infection were not statistically significant after using a logistic regression model of multivariate analysis.

Other information about some factors known to influence the mortality of septicemia, such as the initial site of infection, shock, DIC or the presence of multiple organ system dysfunction, was not available for analysis in this study.

In conclusion, mortality in septicemia in children can be reduced by the use of appropriate antimicrobial agents and effective control of the infection in the compromised host and in newborn patients.

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