Prognostic indicators of septicaemia – a two year prospective evaluation

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Summary: The problem of septicaemia in a district general hospital was studied prospectively over a two year period, with respect to factors affecting prognosis. Age had little influence on the outcome, although several factors showed age-related trends which tended to be unfavourable to survival. The mortality among patients over 65 years of age was 39.5% and this was not significantly different from the mortality of 34.5% among those below that age. It is suggested that by taking into consideration simple clinical and laboratory findings like sex, source of infection, intercurrent illness, blood urea, pulse rate and temperature, it is possible to predict prognosis with reasonable accuracy without recourse to excessive expenditure of money or resources.

Introduction

Blood cultures are one of the most important procedures for the detection of systemic infection. Several studies have examined various aspects of septicaemia in adults, but studies to identify prognostic indicators have been sparse and the few retrospective analyses have only dealt with the extent of the problem¹ and the general prognosis.² In this prospective study we present our experience with septicaemia in hospitalized elderly patients as compared with younger in-patients. The prognostic parameters of septicaemia have been identified and evaluated.

Materials and methods

During a two year prospective study period (1982–1984), all in-patients with positive blood cultures for clinically significant bacterial or fungal infections were identified and related to age and sex of patient, host factors, sources of infections, nature of organisms and prognosis.

To determine whether or not the positive culture represented true infection, and to obtain uniformity of interpretation, each patient was evaluated independently by 4 observers. The criteria for inclusion of a patient in the study were the clinical state of the patient, the same organism being isolated from more than one source and/or from more than one blood culture together with a consideration of pulse rate and

presence or absence of pyrexia ($> 37.5^{\circ}\text{C}$). Information considered difficult to interpret was discussed among the observers separately and a majority decision was accepted.

Apart from documenting clinical findings, day to day progress and relevant investigations on individual patients, a full blood count, erythrocyte sedimentation rate, and plasma glucose were determined together with a biochemical profile (estimated by a S.M.A.C. Autoanalyser: Technicon Inc.) whenever a blood culture was taken. Aerobic and anaerobic blood cultures were taken in commercially available ¹⁴C-labelled tryptic soy broth (Bactec, Becton, Dickinson & Co., Maryland, USA) and the results read at 12, 24, 48 hours, and at 7 days. An episode of bacteraemia/fungaemia was defined by the 1st positive blood culture or a new blood culture becoming positive more than 7 days after the date the preceding blood culture was taken. Breakthrough septicaemia³ as well as any blood culture becoming positive within 7 days of a previous positive blood culture was considered to represent the same episode.

All information obtained on an individual patient was recorded on specially designed coded sheets to facilitate computerization and analysis. The results were analysed using a CDC7600 computer and statistical comparisons were performed by the Mann-Whitney U test and the Chi-square test with continuity correction using the SSPS Package.⁴ Further analysis of risk factors was performed by using a stepwise logistic regression (maximum likelihood ratio) taken from the BMD Package.⁵

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Figure 1 Age and sex distribution of patients with septicaemia; ■, male; □, female.

Results

There were 137 episodes of septicaemia in 129 patients in this study. Age and sex distribution is shown in Figure 1 and the relation of the episodes to the outcome is summarized in Table I. The youngest patient was 15 years old and the oldest 91 years. Two thirds of the patients were over 65 years of age, and 70 years was the median age in that it separated the population of the patients into equal halves. It is obvious from Table I that the mortality in the age groups above and below 65 years is similar (39.5% and 34.9% respectively), and comparable with the overall mortality of 38%. However, the mortality of 47.9% in the females is significantly different from that of 25.9% in the males ($P = 0.019$). This increased mortality in the female population is reflected particularly in the over 65 years age group.

Positive results were obtained with 137 blood cultures of which 17 yielded mixed Gram-positive and Gram-negative organisms (Table II). Thirty-six per cent of the total were Enterobacteriaceae, *Escherichia coli* accounting for over two thirds of this group. Forty-two per cent of blood cultures yielded Gram-positive cocci; just over a quarter of this group were

Table I Relationship between survival prospects and age and sex in a series of patients with septicaemia.

		< 65 years	> 65 years	Total
Males	N	23	35	58
	D	7 (30.4)*	8 (22.8)**	15 (25.9)***
Females	N	20	51	71
	D	8 (40.0)*	26 (51.0)**	34 (47.9)***
Total	N	43	86	129
	D	15 (34.9)	34 (39.5)	49 (38.0)

N = number of patients; D = number dead; numbers in parenthesis indicate % of N.

* P not significant, comparing males and females under 65 years age.

** $P < 0.01$ comparing males and females over 65 years age.

*** $P < 0.02$ overall comparison of males and females.

Staphylococcus aureus, almost two fifths were *Staphylococcus epidermidis* and over one fifth of the group were pneumococci. Bacteroides spp. accounted for only 4% of all positive blood cultures and a miscellaneous group which included *Neisseria meningitidis*, fungi and mixed organisms (Gram-negative bacilli and

Table II Organisms isolated from the blood cultures of 129 patients with septicaemia.

Organism	Number of positive blood cultures
Enterobacteriaceae	49 (36%)
<i>Staphylococcus aureus</i>	15 (11%)
<i>Staphylococcus epidermidis</i>	22 (16%)
<i>Streptococcus pneumoniae</i>	13 (9%)
<i>Streptococcus</i> spp.	8 (6%)
<i>Bacteroides</i> spp.	6 (4%)
Miscellaneous*	24 (18%)

*Includes 17 positive cultures of mixed Gram-positive and Gram-negative organisms.

Table III Source of the infection together with outcome in a series of 129 patients with septicaemia.

Source	n	Survivors	(%)
Bowel*	4	4	(100)
Bone	4	2	(50)
Intravenous catheter	7	5	(71)
Biliary tract*	11	8	(73)
Abscess	12	7	(58)
Genito-urinary	38	29	(76)
Respiratory tract	39	20	(51)
Unknown	45	24	(53)

*Organisms isolated from wound drainage associated with gut or biliary tract.

n = number of sources of septicaemia identified.

faecal streptococci) comprised the remaining 18%.

Table III lists the sources of bacteraemia and their influence on mortality. In some patients the organisms from blood cultures originated from more than one source simultaneously. It is obvious that patients with septicaemia of respiratory source had the poorest prognosis with a mortality of almost 50% and those with genito-urinary source, the least mortality (<25%). The influence of factors considered to predispose patients to septicaemia was analysed to determine their effect on prognosis. A total of 9 clinical groups, including a large miscellaneous category, was identified and it is evident that those with haematological malignancy form a particularly high risk category of patients (Table IV).

The analysis of risk factors taken individually showed that a good chance of survival was associated with low blood urea ($P < 0.001$), absence of haematological malignancy ($P = 0.027$), male sex ($P = 0.031$), low pulse rate ($P = 0.037$) and high temperature ($P = 0.050$). The nature of the organism causing the septicaemia did not reach significance as a prognostic factor, nor did an unknown source. The high mortality of this group was related to other risk factors such as high blood urea.

Table IV Factors pre-disposing to septicaemia together with outcome in a series of 129 patients

Condition	n	Survivors	(%)
Cirrhosis	1	1	(100)
Trauma	4	4	(100)
Haematological malignancy	7	1	(14)
Steroid therapy	15	6	(40)
Other neoplasms	17	9	(53)
Surgery	20	15	(75)
Diabetes mellitus	20	12	(60)
Uraemia	21	12	(57)
Others	44	24	(55)

n = number of associated conditions identified in the series.

Table V Clinical features associated with septicaemia that favour survival, derived from an analysis of survival as a function of clinical and laboratory findings using stepwise logistic regression. Death or survival was correctly predicted in 71% of cases using a combination of these risk factors.

Clinical features	Significance as survival P factor
Low blood urea	< 0.001
Absence of haematological malignancy	= 0.007
Normal haemoglobin	= 0.015
Male sex	= 0.019
Low pulse rate	= 0.030
Pyrexia	= 0.041
Genito-urinary source of infection	= 0.042

A stepwise logistic regression was used to select a group of variables which could be used to predict death or survival (Table V). In 71% of cases the outcome would have been correctly predicted on the basis of the values taken by these variables. Of the 29% incorrectly predicted 23 patients survived and 14 were non-survivors.

Discussion

This study identified no significant influence of age on the outcome of septicaemia. Similar results are noted in the series of Setia & Gross,⁶ where mortality ranging from 39 to 43% has been recorded in different age groups from 40 years upwards. In their series however, a much reduced mortality is reported in the age group 0–39 years but details of the distribution of ages in this group were not given and therefore no useful comparison could be made with the younger age group of the present study. Both our findings and those of Setia & Gross differ sharply with the conclusions of other studies, where an increased mortality related to age has been found.^{2,7,8} In these other studies, the proportion of patients with septicaemia who died from intercurrent causes has not been given and this might explain the discrepancy between the sets of results. We did find, however, that two factors, haemoglobin and blood urea, tended towards levels unfavourable to survival in the group of patients above the median age of 70 years, although we regarded these as age-related trends rather than those precipitated by infection.

One of the interesting observations in our study was the finding of a significantly increased mortality in female as compared with male patients. There have been only a few reports that comment on sex difference on the outcome of septicaemia; in contrast with our findings, Weinstein *et al.*² noted an increased risk for males in their study.

The similarity of distribution of organisms involved across the different age groups made it possible to study their role in the outcome of septicaemia. Higher mortality has been reported to be associated with Gram-negative organisms as compared with Gram-positive bacteria^{9,10,11} although, in contrast, Gram-positive organisms have been implicated with higher mortality by other workers.^{12,13} This study, however, was unable to identify prognostic risk in terms of nature of the organism; and this conclusion concurs with that of Setia & Gross.⁶ It is suggested that although an individual organism may exert a sig-

nificant influence on the outcome in a given patient, the organism itself has little predictive value in prognosis when all other risk factors are also taken into consideration (Table V). Empirical and then specific antimicrobial therapy was carried out on all patients in this series immediately it was realized that septicaemia was occurring. The delay in commencing therapy in each case was minimal since a radio-isotope method is employed to monitor all blood cultures sent to the Microbiology Laboratory.

This series identified the most common lethal source of septicaemia as respiratory tract infections, the most favourable outcome being in those originating from the genito-urinary tract; other reports support this observation.^{2,6,14} In about one third of all the septicaemic patients the source was unknown and this finding is similar to that of other reports.^{15,16} Dupont & Spink⁹ as well as Hodkin & Sanford¹⁷ found no effect of temperature on the outcome of septicaemia. In contrast, failure to mount a pyrexia greater than 37.5°C was found in our study to be associated with an increase in mortality, a finding in agreement with those of several other investigators.^{16,18,19} Hypotension has been recognized as an important risk factor in septicaemia;^{16,20} in our study, however, this parameter did not attain statistical significance, although pulse rate appeared to have an influence on the outcome.

Many diseases, chemotherapeutic agents, and procedures have been alleged to increase the incidence of septicaemia and its mortality.^{9,16,18} While several factors in our study were found to predispose to septicaemia, those which significantly influenced the outcome were haematological malignancy and impaired renal function. It is, of course, possible that other factors occurred as the sole pre-disposing condition too infrequently for them to reach statistical significance.

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References

- Williams, G.T., Houang, E.T., Shaw, E.J. & Tabachali, S. Bacteraemia in a London teaching hospital 1966–75. *Lancet* 1976, **ii**: 1291–1293.
- Weinstein, M.P., Murphy, J.R., Reller, L.B. & Lichtenstein, K.A. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults II. Clinical observations with special reference to factors influencing prognosis. *Rev Infect Dis* 1983, **5**: 54–70.
- Anderson, E.T., Young, L.S. & Hewitt, W.L. Simultaneous antibiotic levels in "breakthrough" gram-negative bacteremia. *Am J Med* 1976, **61**: 493–497.
- Hull, C.H. & Nie, N.H. In *SSPS Update*. 7–9, McGraw Hill, New York, 1981, 233.
- Dixon, W.J. *BMDP Statistical Software Manual*, University of California Press, Berkeley, 1985, 330–343.
- Setia, U. & Gross, P.A. Bacteremia in a community hospital. *Arch Intern Med* 1977, **137**: 1698–1701.
- McGowen, J.E., Barnes, M.W. & Finland, M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972), with special reference to hospital acquired cases. *J Infect Dis* 1975, **132**: 316–335.
- Chattopadhyay, B. & Al-Zahawi, M. Septicaemia and its

- unacceptably high mortality in the elderly. *J Infect* 1983, **7**: 134–138.
9. Dupont, H.L. & Spink, W.W. Infections due to Gram-negative organisms: an analysis of 860 patients with bacteremia at University of Minnesota Medical Centre, 1958–1966. *Medicine* 1969, **48**: 307–332.
 10. Wolff, S.M. & Bennett, J.V. Gram-negative rod bacteremia (Editorial). *N Engl J Med* 1974, **291**: 733–734.
 11. Spengler, R.F., Greenough, W.B. & Stolley, P.D. A descriptive study of nosocomial bacteremia at the Johns Hopkins Hospital, 1968–1974. *Johns Hopkins Med J* 1978, **142**: 77–84.
 12. Kluge, R.M. & Dupont, H.L. Factors affecting the mortality of patients with bacteremia. *Surg Gynecol Obstet* 1973, **137**: 267–269.
 13. Charles, M.N., Beaty, H.M. Staphylococcus aureus bacteremia: *Am J Med* 1976, **60**: 495–500.
 14. McCabe, W.R. & Jackson, G.G. Gram-negative bacteremia. I. Etiology and ecology. *Arch Int Med* 1962, **110**: 847–855.
 15. Myerowitz, R.L., Medeiros, A.A. & O'Brien, T.F. Recent experience with bacilleemia due to Gram-negative organisms. *J Infect Dis* 1971, **124**: 239–246.
 16. Kreger, B.E., Craven, D.E., Carling, P.C. & McCabe, W.R. Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. *Am J Med* 1980, **68**: 332–343.
 17. Hodkin, U.G. & Sanford, J.P. Gram-negative bacteremia: an analysis of 100 patients. *Am J Med* 1965, **39**: 952–960.
 18. Bryant, R.E., Hood, A.F., Hood, C.E. & Koenig, M.G. Factors affecting mortality of Gram-negative rod bacteremia. *Arch Int Med* 1971, **127**: 120–128.
 19. Montgomerie, J.Z. & Ota, J.K. Klebsiella bacteremia. *Arch Int Med* 1980, **140**: 525–527.
 20. Scheckler, W.E. Septicemia in a community hospital, 1970–1973. *JAMA* 1977, **237**: 1938–1941.