Metastatic Complications of *Staphylococcus aureus* Septicemia. To Seek is to Find

H. Ringberg, A. Thorén, B. Lilja

Summary

Improvement in the high mortality from *Staphylococcus aureus* septicemia must address the individualized treatment (surgery and/or prolonged antibiotic treatment) of metastatic complications. The aim of this study was to evaluate the results of a comprehensive diagnostic monitoring for metastatic complications in *S. aureus* septicemia. 68 consecutive patients with *S. aureus* septicemia were prospectively followed. The performance rate and results of chest X-ray, echocardiography, bone scintigraphy and leukocyte scintigraphy are described. Metastatic complications were found in 53% of the 68 patients, endocarditis in 26%. Positive findings resulted in surgical intervention in 23 patients. The total mortality defined as all deaths within 12 weeks was 24%; 81% of the deceased were ≥ 60 years of age. Non-endocarditis patients with peripheral septic metastases had good prognosis.

An active monitoring for metastatic complications in *S. aureus* septicemia is a necessary prerequisite for optimizing treatment and to improve survival rate.

Key Words

***Staphylococcus aureus* · Septicemia · Endocarditis · Septic metastases · Mortality**

Infection 2000;28:132–136

Introduction

Septicemia caused by *Staphylococcus aureus* is still associated with a high mortality despite the availability of specific antistaphylococcal antibiotics for more than 20 years [1, 2]. In a retrospective study by *Kuikka* and *Valtonen* the improved outcome during recent years was attributed to the addition of an aminoglycoside to treatment with isoxazolyl penicillins [3], although no controlled study has been able to substantiate this [4, 5]. Mortality is known to be related to background factors such as advanced age, underlying diseases and unidentified primary focus [2, 6–9]. Moreover, complications such as endocarditis with secondary metastatic foci are associated with a high mortality (30–68%) especially in non-drug addicts [8, 10, 11]. Endocarditis with or without other metastatic foci necessitates prolonged, initially combined iv antibiotic treatment and frequently surgery. While it is important to identify metastatic complications in *S. aureus* septicemia in order to optimize treatment, the reported frequency of such complications varies greatly, 2–47% [2, 6, 11–15]. One explanation may be the level of investigative activity, for instance the use of echocardiography for the detection of endocarditis [16, 17].

To improve the outcome of staphylococcal septicemia, a consecutive prospective study with comprehensive monitoring for septic complications in 68 patients was initiated.

Materials and Methods

Somatic inpatients in the city of Malmö (240,000 inhabitants) with fever or other signs of non-surgical infection are as a rule treated at the Department of Infectious Diseases, Malmö University Hospital. The present study was carried out at the department during the period of November 1988 through June 1992.

History and Physical Examination of Patients

Concurrent diseases including diabetes, asthma, chronic obstructive lung disease, rheumatoid arthritis, uremia, heart failure and immune deficiencies were recorded for all patients, as was drug abuse, hypersensitivity to antibiotics, preceding antibiotic therapy and duration of fever. The patients were regularly examined for the presence of fever, cardiac murmurs, and signs of arterial emboli to the conjunctival membrane, nail bed and skin.

Cultures

Blood cultures were repeatedly performed after initiation of treatment, normally for 2 days or longer in case of persistent signs of septicemia. Cultures were also made from urine and with swabs or sterile puncture from suspected foci when appropriate.

H. Ringberg *(corresponding author)*, **A. Thorén**
Dept. of Infectious Diseases, Lund University, Malmö University Hospital, S-205 02 Malmö, Sweden; Phone +46-40-331000; Fax: +46-40-336279, e-mail: Hakan.Ringberg@inf.mas.lu.se
B. Lilja
Dept of Clinical Physiology, Lund University, Malmö University Hospital, S-205 02 Malmö, Sweden

Received: October 5, 1999 • Revision accepted: February 8, 2000

Table 1
Baseline data for 68 patients with *Staphylococcus aureus* septicemia.

Mean age (range)	54 (13–88)
Sex (male/female)	30 / 38
Underlying diseases	39 (57%)
Alcohol abuse	10 (15%)
Asthma/chronic obstructive lung disease	9 (13%)
Diabetes	8 (12%)
Congestive heart failure	7 (10%)
Rheumatoid arthritis	6 (9%)
Uremia	4 (6%)
Immune deficiency	4 (6%)
Nosocomial infection	22 (32%)
Iv drug abuse	12 (18%)
Other community acquired infection	34 (50%)
Mean (range) C-reactive protein (mg/l)	182 (10–450)
Mean (range) WBC count (10^9/l)	12 (1–28)
Mean (range) hemoglobin (g/l)	117 (78–166)
Mean (range) platelet count (10^9/l)	227 (34–768)
Mean (range) creatinine (µmol/l)	140 (52–907)
Mean (range) ALAT (µkat/l)	1.2 (0.1–17.8)

Blood cultures and antibiotic sensitivity testing of all isolates were performed by standard methods as previously described [18].

Other Laboratory Tests

All patients were followed with blood examinations including platelet-, white blood cell- and differential count, hemoglobin, ESR, CRP, serum electrolytes, creatinine and aminotransferases at inclusion and up to three times weekly. Patients treated with aminoglycosides were monitored with serum concentrations three times weekly.

X-Ray and Clinical Physiological Studies

X-ray of lungs, echocardiography (UCG), scintigraphy of bones and scintigraphy of leukocytes were performed as appropriate after inclusion. The examinations were repeated after 2 weeks, when indicated.

UCG was performed transthoracically using a Diasonics CV 400 or a HP Sonos 1000.

Bone scintigraphy was carried out as follows: Approximately 600 MBq ^{99m}Tc-MDP were injected iv and whole body scanning was performed after 3 h, using a Toshiba GCA901A gamma camera.

Leukocyte scintigraphy was done using mixed leukocytes labelled with 200 mBq ^{99m}Tc-HMPAO using a slightly modified method developed at Hammersmith Hospital [19]. Whole body scanning was performed 3 and 24 h after injection on a Toshiba GCA901A gamma camera equipped with an LEGP collimator. If a positive finding was made, a 360° tomography was performed over the target area.

Definitions

***S. aureus* Septicemia.** A patient with at least one positive blood culture and associated clinical signs of infection such as fever, chills and/or hypotension/shock [6].

Mortality. All deaths within 12 weeks.

Endocarditis. Patients were considered to have endocarditis if UCG showed vegetations as described in the Duke scheme [20, 21], if autopsy showed pathologic evidence of endocarditis or if the patient had typical multiple, rounded septic foci on chest X-ray [22].

Treatment

Parenteral treatment was normally given for 14 days followed by oral treatment in a median duration of 6 weeks. Patients with endocarditis received 4 weeks of parenteral treatment only. The standard parenteral antibiotics were cloxacillin + netilmicin followed by oral flucloxacillin. The alternative treatments included vancomycin or rifampicin + clindamycin. No differences were observed regarding the efficacy or rate of side effects between these regimens.

Results

Baseline data for the 68 patients are shown in table 1. The mean age was 54 years (range 13–88 years). Only 32% had a nosocomial infection. 18% were intravenous drug addicts but as much as 50% of all patients had community acquired infections and had no history of iv abuse.

Foreign body infections occurred in two patients with infected hip prosthesis (removed at inclusion and on day 5, respectively) and nine patients with intravascular devices. These were routinely removed at inclusion or in two patients with Port-A-Cath, by surgery at day 6 and 136, respectively. The last operation was delayed for technical reasons but the infection was stable within a few days.

The clinical symptoms and signs were those commonly seen in septicemia with chills and spiking fever and sometimes hypotension. Generalized muscular-skeletal pain was common.

Table 2
Results of screening methods for septic metastases and occurrence of following surgery and/or prolonged antibiotic treatment (n = 68 patients).

	No. of screened patients	Positive screening results	Operated patients due to screening method	Prolonged treatment due to screening method
Skin examination	68 (100%)	11/68 (16%)	9/68 (13%)	2/68 (3%)
Chest X-ray	57 (84%)	15/57 (26%)	1/57 (2%)	7/57 (12%)
UCG	45 (66%)	15/45 (33%)	1/45 (2%)	13/45 (29%)
Bone scintigraphy	31 (46%)	19/31 (61%)	9/31 (29%)	10/31 (32%)
Leukocyte scintigraphy	16 (24%)	4/16 (25%)	3/16 (19%)	2/16 (13%)

The mean duration of fever in the 52 surviving patients was 6.5 days, maximum 32 days. Patients who underwent surgical treatment had a mean fever duration of 9.4 days.

Blood cultures were regularly drawn for at least 2 consecutive days after initiation of treatment. 21 had positive blood cultures days 2–6. Only one of 68 blood culture isolates was resistant to methicillin (MRSA).

No case of relapse was observed at the scheduled 3-month follow-up.

Septic Metastases

The screening activity for septic metastases and the resulting surgical interventions and/or prolonged antibiotic treatment are shown in table 2. The performance rate was: chest X-ray 84%, UCG 66%, bone scintigraphy 46% and leukocyte scintigraphy 24% of all patients. Septic metastases were detected in 36 of all 68 patients (53%). The 67 different septic foci were distributed as follows: bones 18, heart valves 16, lungs 15, joints 6 and other localities 12.

Multiple septic metastases were most common in connection with endocarditis: more than one peripheral septic metastasis was detected in 9/18 (50%) of patients with endocarditis but only in four of the remaining 50 patients (8%).

Signs of infection in bone and deeply situated soft tissues, such as the psoas region, were followed up with focal investigations as conventional X-ray, ultrasound investigation, computerized tomography (CT) and magnetic resonance imaging (MRI). These investigations were performed to precede surgical interventions which often could be effected by puncture guided by X-ray. 23 patients were subjected to one or several surgical interventions.

Endocarditis was diagnosed in 18 patients, by UCG in 15 patients, at autopsy with a previously normal UCG in two patients and by a typical chest X-ray with multiple, rounded septic foci despite a normal UCG in one patient.

Intravenous drug abuse was recorded in 5/18 patients with endocarditis. Three had right-side, and two left-side endocarditis.

The mortality in endocarditis patients with iv drug abuse was 0% and in non-iv abusers 46%.

Surgical Intervention

This included heart valve surgery (one patient), removal of infected hip prosthesis (two patients), draining of psoas abscesses (four patients), puncture or incision in bone and joints (13 patients) and incision of abscesses in soft tissue in three additional patients. The surgical intervention normally resulted in resolution of fever.

Mortality

The total mortality was 24%. Table 3 shows that mortality is related to age, unknown origin of primary focus and to endocarditis, with the exception of patients with iv drug abuse. Statistical calculation by the chi-square test and Fisher's exact test will only demonstrate a significant association of mortality to age ($p < 0.01$, Fisher's exact test, two-tailed).

Table 3
Mortality, all patients (n = 68).

Patient category:	Nosocomial septicemia	27%
	Iv drug abuse	0%
	Other community acquired septicemia	29%
Primary focus:	Known	20%
	Unknown	33%
Age (years):	< 60	9%
	≥ 60	37%
Endocarditis:	All	33%
	Iv drug abuse	0%
	No iv drug abuse	46%

Statistical comments in text

Half of the 16 deaths occurred within the first 2 weeks (mean 4 days), the rest between 15 days and 3 months (mean 31 days).

A detailed presentation of mortality in relation to age, endocarditis and peripheral septic metastases is shown in figure 1. Only three patients under 60 years of age died, a 28-year-old uremic man with immune suppressive therapy because of kidney transplant rejection, a 50-year-old male alcoholic with severe asthma and a 52-year-old formerly

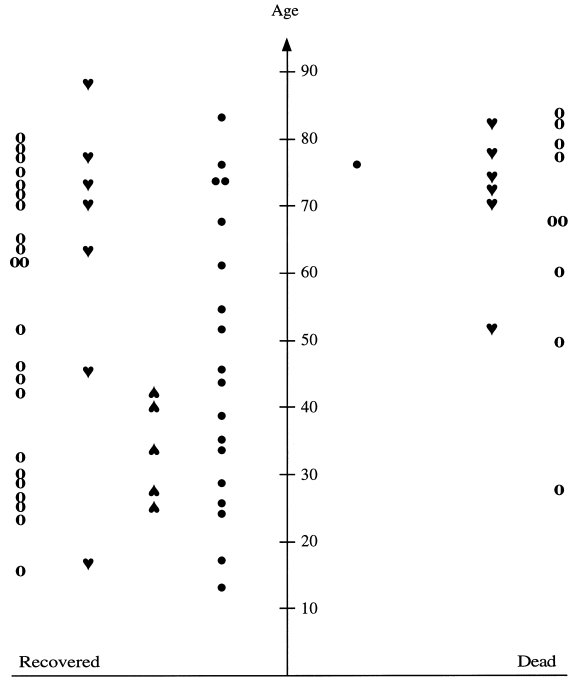

Figure 1
Recovered/dead patients in relation to age and type of septic metastases.
O = No septic metastases (n = 31)
♥ = Endocarditis without iv drug abuse (n = 13)
▲ = Endocarditis and iv drug abuse (n = 5)
● = Peripheral septic metastases without endocarditis (n = 19)

healthy man whose septicemia was complicated by endocarditis and septic metastases to lungs and skin; he died of a massive cerebral hemorrhage. In non-endocarditis patients the occurrence of septic metastases did not enhance mortality: only one of 19 patients with peripheral septic metastases died compared to nine of 31 without.

Postmortem Examinations

Autopsy was performed in 11 of the 16 patients who died. Endocarditis was demonstrated in five of these, having been previously undiagnosed in two.

Discussion

The 68 patients represented a selected group since they were either referred from other departments due to the severe septic disease or directly admitted to the Department of Infectious Diseases with, for instance, fever of unknown origin. A large number of patients (50%) had community acquired infections, even when intravenous drug addicts, having a good prognosis due to low age [8], were excluded. Considering this selection, the total mortality of 24% appears low.

In Sweden, the low incidence of septicemia caused by MRSA strains is still valid in 1999 due to determined efforts by the Units of Infectious Diseases to eliminate imported MRSA strains.

Lautenschlager et al. stress the importance of access to specialists for infectious diseases for a successful outcome of treatment. They mainly refer to the importance of correct interpretation of blood culture results followed by an appropriate initial antibiotic treatment [11]. The latter is obviously an essential prerequisite and has lowered the mortality rate from about 80% in the 1940s [23] to currently reported rates of about 30%. A further improvement of survival must address the diagnosis and treatment of complications such as septic metastases necessitating prolonged iv treatment or surgical intervention [24].

Bayer et al. have prospectively studied 72 and 63 patients, respectively, to evaluate the validity of different diagnostic criteria for endocarditis. UCG was reported to have the highest validity [16, 21]. In this study UCG was performed transthoracically. Transesophageal UCG used today should further enhance the detection rate of endocarditis [17]. *Mylotte* et al. reported a mortality rate of 32% in their carefully conducted prospective study of 114 patients [6], but only two were found to have endocarditis (2% versus 26% in our investigation). Since the diagnosis in that study was only based on clinical criteria and not on UCG, an underestimation of the number of cases of endocarditis could explain the high mortality. The authors are aware of this and have consequently suggested that iv antibiotic treatment should be routinely prolonged to 4–6 weeks in patients with community acquired infection without a definable focus. The duration could be limited to 2–3 weeks in the absence of clinical risk factors for endocarditis or other specified complications. Such a treatment policy, however, may result in expensive and potentially harmful overtreatment in many patients.

In this presentation of *S. aureus* septicemia we have focused on development of septic metastases with or without concurrent endocarditis. We have demonstrated that intensive diagnostic activity results in a high detection rate of septic metastases, 53% of the patients. Septic metastases surprisingly often necessitate surgical intervention. In other clinical contexts, for instance abscesses in unattainable locations such as liver or brain, conservative treatment with antibiotics is preferred but necessitates protracted and intensive treatment [25]. Obviously septic metastases in staphylococcal septicemia will require more than an adequate initial antibiotic treatment. Antibiotic treatment was normally administered for 8 weeks in the present investigation. Since the antibiotic treatment after the first 2 weeks could be continued outside the hospital, the duration of hospital care in surviving patients was not prolonged.

In summary, this study has confirmed the high mortality risk in non-addicts with endocarditis. A comprehensive diagnostic activity has revealed a high incidence of endocarditis and peripheral septic metastases. This knowledge is a necessary prerequisite for a tailored antibiotic therapy and surgery.

Acknowledgment

This investigation was supported by grants from the Medical Faculty, Lund University (90/12).

References

1. McGowan JE Jr, Barnes MW, 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.
2. Willcox PA, Rayner BL, Whitelaw DA: Community-acquired *Staphylococcus aureus* bacteraemia in patients who do not abuse intravenous drugs. Q J Med 1998; 91: 41–47.
3. Kuikka A, Valtonen VV: Improved outcome of *Staphylococcus aureus* bacteremia. Infect Dis Clin Pract 1994; 3: 282–287.
4. Korzeniowski O, Sande MA, The National Collaborative Endocarditis Study Group: Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts. Ann J Med 1982; 97: 496–503.
5. Watanakunakorn C, Baird IM: Prognostic factors in *Staphylococcus aureus* endocarditis and results of therapy with a penicillin and gentamicin. Am J Med Sci 1977; 273: 133–139.
6. Mylotte JM, McDermott C, Spooner JA: Prospective study of 114 consecutive episodes of *Staphylococcus aureus* bacteremia. Rev Infect Dis 1987; 9: 891–907.
7. Gransden WR, Eykyn SJ, Phillips I: *Staphylococcus aureus* bacteraemia: 400 episodes in St. Thomas's Hospital. Br Med J 1984; 288: 300–303.
8. Julander I: Unfavourable prognostic factors in *Staphylococcus aureus* septicemia and endocarditis. Scand J Infect Dis 1985; 17: 179–187.

9. McClelland RS, Fowler VG, Sanders LL, Gottlieb G, Kong LK, Sexton DJ, Schmader K, Lanclos KD, Corey GR: *Staphylococcus aureus* bacteremia among elderly vs younger adult patients. Comparison of clinical features and mortality. Arch Intern Med 1999; 159: 1244–1247.
10. Hedström SÅ, Christensson B: *Staphylococcus aureus* septicaemia and endocarditis at the University Hospital in Lund 1976–1980. Scand J Infect Dis Suppl 1983; 41: 38–46.
11. Lautenschlager S, Herzog C, Zimmerli W: Course and outcome of bacteremia due to *Staphylococcus aureus*: evaluation of different clinical case definitions. Clin Infect Dis 1993; 16: 567–573.
12. Nolan CM, Beaty HN: *Staphylococcus aureus* bacteremia. Current clinical patterns. Am J Med 1976; 60: 495–500.
13. Perrotin D, Nyongabo T, Choutet P, Baron D, Breux JF, Chennebault JM, Loustaud V: Septicémies primitives à staphylocoques de l'adulte. Etude rétrospective. Presse Med 1989; 18: 573–576.
14. Cunney RJ, McNamara EB, AlAnsari N, Smyth EG: Community and hospital acquired *Staphylococcus aureus* septicaemia: 115 cases from a Dublin teaching hospital. J Infect 1996; 33: 11–13.
15. Finkelstein R, Sobel JD, Nagler A, Merzbach D: *Staphylococcus aureus* bacteremia and endocarditis: comparison of nosocomial and community-acquired infection. J Med 1984; 15: 193–211.
16. Bayer AS, Lam K, Ginzton L, Norman DC, Chiu CY, Ward JI: *Staphylococcus aureus* bacteremia. Clinical, serologic, and echocardiographic findings in patients with and without endocarditis. Arch Intern Med 1987; 147: 457–462.
17. Fowler VG, Sander LL, Kong LK, McClelland RS, Gottlieb GS, Li J, Ryan T, Sexton DJ, Roussakis G, Harrel LJ, Corey GR: Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. Clin Infect Dis 1999; 28: 106–114
18. Ringberg H, Thorén A, Bredberg A: Evaluation of coagulase-negative staphylococci in blood cultures. A prospective clinical and microbiological study. Scand J Infect Dis 1991; 23: 315–323.
19. Roddie ME, Peters AM, Danpure HJ, Osman S, Henderson BL, Lavender JP, Carroll MJ, Neirinck RD, Kelly JD: Inflammation: imaging with Tc-99m HMPAO-labeled leukocytes. Radiology 1988; 166: 767–772.
20. Durack DT, Lukes AS, Bright DK, the Duke Endocarditis Service: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994; 96: 200–209.
21. Bayer AS, Ward JI, Ginzton LE, Shapiro SM: Evaluation of new clinical criteria for the diagnosis of infective endocarditis. Am J Med 1994; 96: 211–222.
22. Julander I, Arneborn P, Bäck E, Höglund C, Svanbom M: Intravenous drug addiction – staphylococcal septicemia – pulmonary embolism: a triad pathognomonic for tricuspid valve endocarditis? Scand J Infect Dis 1983; 15: 257–265.
23. Skinner D, Keefer CS: Significance of bacteremia caused by *Staphylococcus aureus*: a study of one hundred and twenty-two cases and a review of the literature concerned with experimental infection in animals. Arch Intern Med 1941; 68: 851–875.
24. Fowler VG, Sander LL, Sexton DJ, Kong L, Marr KA, Gopal AK, Gottlieb G, McClelland RS, Corey GR: Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis 1998; 27: 478–486.
25. Bamberger DM: Outcome of medical treatment of bacterial abscesses without therapeutic drainage: review of cases reported in the literature. Clin Infect Dis 1996; 23: 592–603.