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Levofloxacin does not decrease mortality in *Staphylococcus aureus* bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients

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Abstract. Ruotsalainen E, Järvinen A, Koivula I, Kauma H, Rintala E, Lumio J, Kotilainen P, Vaara M, Nikoskelainen J, Valtonen V, the FINLEVO Study Group (Helsinki University Central Hospital, Helsinki; Kuopio University Hospital, Kuopio; Oulu University Hospital, Oulu; Satakunta Central Hospital, Pori; Tampere University Hospital, Tampere; Turku University Central Hospital, Turku; and Helsinki University Central Hospital Laboratory, Helsinki; Finland). Levofloxacin does not decrease mortality in *Staphylococcus aureus* bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients. *J Intern Med* 2006; **259**: 179–190.

Objectives. To study whether levofloxacin, added to standard treatment, could reduce the high mortality and complication rates in *Staphylococcus aureus* bacteraemia.

Design. A prospective randomized multicentre trial from January 2000 to August 2002.

Setting. Thirteen tertiary care or university hospitals in Finland.

Subjects. Three hundred and eighty-one adult patients with *S. aureus* bacteraemia. Patients with meningitis, and those with fluoroquinolone- or methicillin-resistant *S. aureus* were excluded.

Interventions. Standard treatment (mostly semisynthetic penicillin) ($n = 190$) or that combined with levofloxacin ($n = 191$). Supplementary rifampicin was recommended if deep infection was suspected.

Main outcome measures. Primary end-points were mortality at 28 days and at 3 months. Clinical and laboratory parameters were analysed as secondary end-points.

Results. Adding levofloxacin to the standard treatment offered no survival benefit. Case fatality rates were 14% in both groups at 28 days, and 21% in the standard treatment and 18% in the levofloxacin group at 3 months. Levofloxacin combination did not differ from the standard treatment in the number of complications, time to defervescence, decrease in serum C-reactive protein concentration or length of antibiotic treatment. Deep infection was found in 84% of patients within 1 week following randomization with no difference between the treatment groups. At 3 months, the case fatality rate for patients with deep infection was 17% amongst those who received rifampicin versus 38% for those without rifampicin

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($P < 0.001$, odds ratio = 3.06, 95% confidence intervals = 1.69–5.54).

Conclusions. Levofloxacin combined with standard treatment in *S. aureus* bacteraemia did not decrease mortality or the incidence of deep infections, nor did it speed up recovery. Interestingly, deep infections in *S. aureus* bacteraemia appeared to be more common than previously reported.

Keywords: bacteraemia, fluoroquinolone, levofloxacin, rifampicin, sepsis, *Staphylococcus aureus*.

Introduction

Staphylococcus aureus is the second most common bloodstream isolate both in hospital and community-acquired bacteraemias in all age groups. *Staphylococcus aureus* bacteraemia (SAB) still confers remarkably high mortality, ranging up to 60% in some studies, although antistaphylococcal antibiotics have been available for more than 40 years [1–4]. During recent decades there has been no significant improvement in the outcome of staphylococcal infections, which cannot be entirely explained by the increased incidence of methicillin-resistant *S. aureus* (MRSA) [5, 6]. The clinical course of SAB is determined by its complications, particularly by the development of deep infections due to metastatic spread, and by the high recurrence rate of bacteraemia [6–12]. The reported frequency of metastatic complications varies greatly, from 10% to 50% [9, 13–16].

The standard treatment strategy for bacteraemic methicillin-sensitive *S. aureus* infections includes a semisynthetic penicillin, such as nafcillin, cloxacillin or dicloxacillin. In endocarditis, an aminoglycoside for 3–14 days is combined with standard treatment [12, 17, 18]. Experimental studies and some small clinical trials suggest that adding rifampicin could improve treatment results in deep infections [19–21], but recommendations on its use are variable [12, 18, 22–24].

Levofloxacin is a fluoroquinolone with improved activity against Gram-positive bacteria including *S. aureus in vitro* [25]. In experimental studies fluoroquinolones have shown an additive effect in combination with standard antistaphylococcal therapy in severe *S. aureus* infections [26]. Furthermore, fluoroquinolones have been combined with rifampicin to provide an entirely oral regimen in staphylococcal right-sided endocarditis [27, 28], chronic osteomyelitis or foreign body infections [29, 30] and other deep-seated abscesses [31]. In SAB, most deep infections are observed within 2 weeks after the onset of bacteraemia [32]. The metastatic complications might be prevented by early treatment with bactericidal fluoroquinolone, which penetrates well into tissues.

We here report the results of the first prospective trial where the effect of levofloxacin in addition to standard antistaphylococcal treatment of SAB was studied in relation to patient outcome and development of complications.

Patients and methods

Study design

This was a prospective, randomized, multicentre trial conducted in five university hospitals and seven tertiary care hospitals in Finland. Adult patients with at least one blood culture positive for *S. aureus* were included within 1–7 days of blood culture sampling from January 2000 through to August 2002. Randomization was done blindly and separately at each study location after the patient or his/her representative had given written informed consent. After randomization, the treatments were open for the investigator and the patient. The trial was approved by the ethics committees of all study sites and by the Finnish National Agency for Medicines.

Exclusion criteria included age younger than 18 years, imprisonment, proven or suspected pregnancy, breastfeeding, epilepsy, another bacteraemia during the previous 28 days, polymicrobial bacteraemia (≥3 microbes), history of allergy to any quinolone antibiotic, previous tendinitis during fluoroquinolone therapy, prior fluoroquinolone use for more than 5 days before randomization, positive culture for *S. aureus* only from a central intravenous catheter, neutropenia ($<0.5 \times 10^9$ L^{-1}) or failure to supply an informed consent. Patients with bacteraemia due to MRSA and a *S. aureus* strain resistant

to any fluoroquinolone, and those with meningitis at the time of randomization, were also excluded.

Study treatments

Patients with SAB were randomly assigned to receive either standard treatment or standard treatment combined with levofloxacin. The dose of levofloxacin was 500 mg once daily for patients under 60 kg and 500 mg b.i.d. for those over 60 kg in weight, both intravenously and orally. Primarily, the standard treatment consisted of a semisynthetic penicillin, cloxacillin or dicloxacillin (2 g q 4 h), intravenously. Alternatively, cefuroxime (1.5 g q 6 h), clindamycin (600 mg q 6–8 h), or vancomycin (1 g b.i.d.) were allowed if a contraindication against the use of penicillins was noted. When oral treatment was indicated, cloxacillin (500 mg q 6 h), cephalexin or cefadroxil (500 mg q 6 h), or clindamycin (300 mg q 6 h) were accepted as standard therapy. In cases of renal dysfunction, the antibiotic doses were adjusted as recommended by the manufacturers.

If endocarditis was clinically suspected or confirmed, aminoglycoside (either tobramycin or netilmicin at 1 mg per kilogram of body weight q 8 h) was added to the drug therapy described above. Rifampicin (450 mg once daily for patients under 50 and 600 mg once daily for patients over 50 kg in weight, orally or intravenously) was given if there was a suspicion or evidence of endocarditis or other deep infections such as pneumonia, deep-seated abscess, osteomyelitis, septic arthritis, mediastinitis or infection of a prosthetic device.

The duration of antibiotic treatment was determined by the treating doctor. However, all patients received at least 14 days of intravenous antibiotic treatment. In SAB associated with a central intravenous catheter the antibiotic treatment was discontinued after 14 days when the catheter was replaced [33]. Parenteral antibiotic therapy was switched to oral dosing after 14 days in patients with no signs of a deep infection, if the serum C-reactive protein (CRP) concentration was <10 mg L^{-1} and the patient was afebrile [13, 16, 34]. When a deep infection was verified or clinically suspected, intravenous antibiotic treatment and rifampicin were recommended to be continued for at least 28 days. In cases of endocarditis, aminoglycoside treatment was discontinued after 7 days [12, 35].

Definitions

Staphylococcus aureus bacteraemia was hospital-acquired if the first positive blood culture was obtained ≥ 48 h after admission, or the patient was a resident in a long-term care facility or attended haemodialysis within the preceding 2 months. Prognosis or severity of underlying diseases were classified as healthy, nonfatal, ultimately or rapidly fatal according to the criteria of McCabe and Jackson [36].

The infection focus was defined as definite if it was documented by bacteriological, radiological or pathological investigations, but suspected if it was evident from clinical findings only. Infection of a central intravenous catheter was defined by the guidelines of the Infectious Diseases Society of America [33]. Endocarditis was classified as definite or possible using the modified Duke criteria [37]. Relapse of SAB was confirmed by the same resistance pattern and pulsed-field gel electrophoresis typing for two *S. aureus* strains. Other recurrences of *S. aureus* culture in the blood were classified as reinfections.

End-points

All patients were followed up by an infectious disease specialist during the hospital treatment and thereafter with control visits at 28 days and at 3 months. Primary end-points were case fatality rate at 28 days and at 3 months. Secondary outcome measures were the number of complications (e.g. deep infections) observed after the first week, decrease in serum CRP concentration, length of antibiotic treatment, need for surgical intervention, and time to defervescence (recorded in days until axillary temperature was <37.5 °C). Laboratory tests were conducted on the day of positive blood culture for *S. aureus*, at randomization and every other day during the first week, twice a week thereafter during hospitalization, at 28 days, and at 3 months.

Sample size and statistical analysis

In the sample size calculation, when mortality was assumed to be 10% in the levofloxacin group and 20% in the standard treatment group, a power of 80% would be achieved with 198 patients in each study arm. A two-tailed significance level of 5% was used.

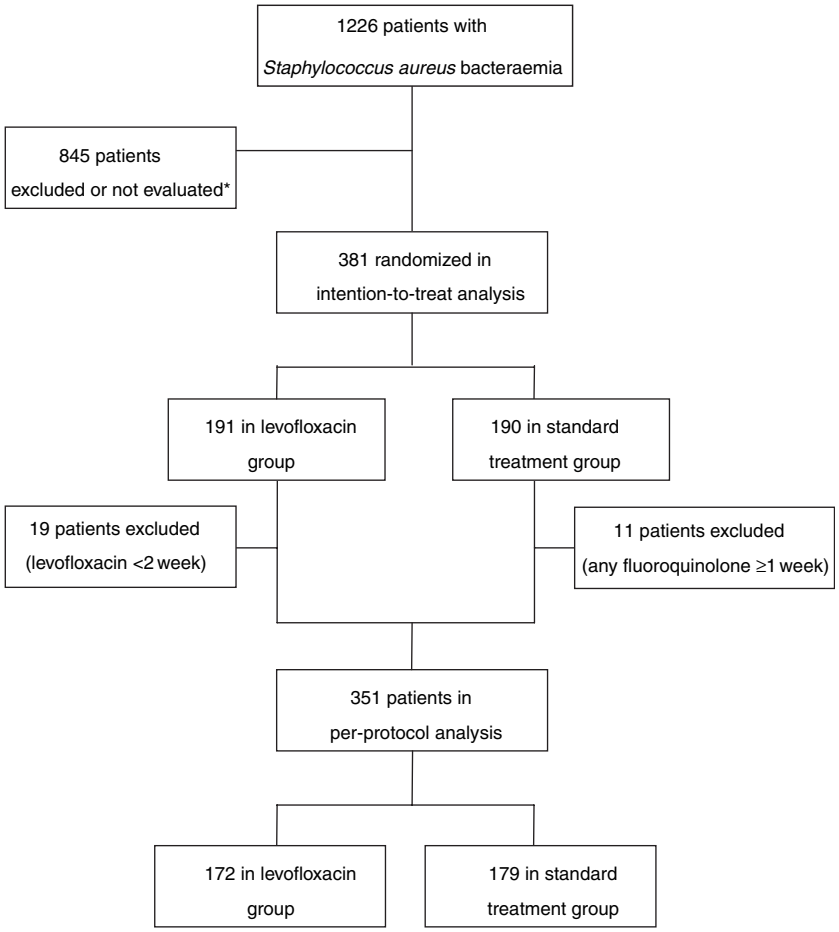

Fig. 1 Study profile. *Not evaluated or excluded patients included 100 patients with failure to supply an informed consent or patient refusal, 48 with neutropenia ($<0.5 \times 10^9$ L^{-1}), 42 deaths prior to randomization, 30 with epilepsy or prior convulsion, 23 with prior fluoroquinolone use for more than 5 days preceding randomization, 15 with a fluoroquinolone resistant strain of *Staphylococcus aureus*, 15 with meningitis, 13 with polymicrobial bacteraemia (≥3 microbes), eight with a positive culture for *S. aureus* only from a central intravenous catheter, seven with another bacteraemia during the previous 28 days, five with bacteraemia due to methicillin-resistant *S. aureus*, three with proven or suspected pregnancy, two prisoners, two breastfeeding, one with a history of allergy to quinolone, one with bacteraemia of borderline oxacillin-resistant *S. aureus*.

Data were analysed from three different patient populations, primarily by intention-to-treat (ITT) analysis with 381 patients. Secondary analysis was performed by per-protocol (PP) (351 patients). Additionally, the length of antibiotic therapy was analysed from a population of which deceased patients were excluded (308 patients). Patients were ineligible for PP analysis if they had received levofloxacin for less than 2 weeks in the levofloxacin group, or any fluoroquinolone for more than 1 week within the first 28 days after randomization in the standard treatment group (Fig. 1).

Statistical analyses were performed with SAS® version 8.2. The primary variable and other categorical variables were analysed with chi-square tests. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the significance of differences in the two treatment groups. The stratified Cochran–Mantel–Haenszel (CMH) test was used in order to adjust for levofloxacin as confounding factor when effect of rifampicin was analysed. Continuous baseline variables were compared using *t*-test. Decrease in serum CRP concentration was analysed using analysis of variance for repeated measurements (RMANOVA). Mortality and time to defervescence survival estimates were calculated with the Kaplan–Meier method. The log-rank test was used to compare the survival estimates. Survival was calculated from the day of randomization until 3 months. All tests were two-tailed, and a $P < 0.05$ was considered significant. Data were analysed at 4Pharma Ltd (Turku, Finland).

Results

Patient characteristics

During the study period, 1226 patients with SAB were identified (Fig. 1). In total, 381 patients were included in the ITT analysis, with 191 patients in the levofloxacin group and 190 patients in the standard treatment group. All collected data except

Table 1 Characteristics and underlying diseases of 381 patients with *Staphylococcus aureus* bacteraemia

Characteristic	Levofloxacin group ($n = 191$)	Standard treatment group ($n = 190$)	Total ($n = 381$)	OR (95% CI)	P
Age (mean years ± SD)	58 ± 19	58 ± 17	58 ± 19	–	0.97
Male sex	116 (61)	121 (64)	237 (62)	1.13 (0.75–1.72)	0.55
Hospital-acquired	102 (53)	105 (55)	207 (54)	1.08 (0.72–1.61)	0.72
Previous skin disease or wound	94 (49)	108 (57)	202 (53)	1.36 (0.91–2.04)	0.14
Prosthetic or intravascular device	63 (33)	66 (35)	129 (34)	1.08 (0.71–1.65)	0.72
Trauma in previous 2 months	51 (27)	49 (26)	100 (26)	0.95 (0.60–1.51)	0.84
Previous surgery[a]	43 (23)	44 (23)	87 (23)	1.04 (0.64–1.67)	0.88
Central intravenous catheter	30 (16)	22 (12)	52 (14)	0.70 (0.39–1.27)	0.24
Intravenous drug abuse[b]	20 (11)	22 (12)	42 (11)	1.12 (0.59–2.13)	0.73
Corticosteroid use ≥1 month	20 (11)	20 (11)	40 (11)	1.01 (0.52–1.94)	0.99
Alcohol abuse	22 (12)	17 (9)	39 (10)	0.76 (0.39–1.47)	0.41
Immunosuppressive therapy[b]	10 (5)	15 (8)	25 (7)	1.55 (0.68–3.55)	0.30
Cardiovascular disease	84 (44)	93 (49)	177 (47)	1.22 (0.82–1.82)	0.33
Diabetes	50 (26)	53 (28)	103 (27)	1.09 (0.69–1.72)	0.71
Chronic lung disease[c]	30 (16)	40 (21)	70 (18)	1.43 (0.85–2.41)	0.18
Chronic renal failure	29 (15)	30 (16)	59 (16)	1.05 (0.60–1.83)	0.87
Hepatic cirrhosis	28 (15)	28 (15)	56 (15)	1.01 (0.57–1.77)	0.98
Autoimmune disease	24 (13)	20 (11)	44 (12)	0.82 (0.44–1.54)	0.53
Cancer	22 (12)	23 (12)	45 (12)	1.06 (0.57–1.97)	0.86
Haematological malignancy	8 (4)	7 (4)	15 (4)	0.88 (0.31–2.46)	0.80
HIV	5 (3)	3 (2)	8 (2)	0.60 (0.14–2.53)	0.48

Values are expressed as n (%), unless otherwise stated. [a]During 3 months preceding the positive blood culture. [b]During 6 months preceding the positive blood culture. [c]Chronic obstructive pulmonary disease, bronchial asthma and other pulmonary disease.

demographic characteristics were analysed in both ITT and PP populations, but only results from ITT analyses are shown.

Patients in the two groups were well matched with respect to demographic characteristics and predisposing conditions (Table 1). When the underlying diseases were grouped by the predicted prognoses (McCabe's classification) [36], 61% of patients had a nonfatal, 27% had an ultimately fatal and 3% had a rapidly fatal disease. Only 9% of the patients were previously healthy. In both groups the median time from sampling of the first positive blood culture to randomization was 3 days.

Antibiotic treatment

All patients were treated with an antibiotic that was effective against *S. aureus* from the time of the first positive blood culture. In ITT analysis, parenteral cloxacillin or dicloxacillin was given to 150 of 191 patients (79%) in the levofloxacin group and to 135 of 190 patients (71%) in the standard treatment group ($P = 0.09$, OR = 0.67, 95% CI = 0.42–1.07). Only 31 patients (16%) in the levofloxacin group and 42 patients (22%) in the standard treatment group were initially treated with cefuroxime with no significant difference between the groups ($P = 0.15$). The treatment groups differed neither in the use of clindamycin or vancomycin. Rifampicin was given significantly more often to patients in the standard treatment group [146 (77%) of 190 patients] than to patients in levofloxacin group [124 (65%) of 191 patients] ($P = 0.01$, OR = 1.79, 95% CI = 1.14–2.81). Combination therapy with an aminoglycoside was also significantly more common in the standard treatment group [44 (23%) of 190 patients] than in the levofloxacin group [20 (11%) of 191 patients] ($P < 0.001$, OR = 2.58, 95% CI = 1.45–4.57).

The median duration of parenteral antibiotic therapy from randomization was 29 days (interquartile range, 22–36 days) in both groups ($P = 0.76$). Levofloxacin was given for a median of 42 days (interquartile range, 28–58 days). Total duration of antibiotic therapy, including intravenous and oral dosing, was for a median of 72 days (interquartile range, 45–85 days) in the levofloxacin group and 80 days (interquartile range,

42–84 days) in the standard treatment group ($P = 0.90$).

Infection foci

At least one deep infection was detected in 331 patients (87%) during the 3 months follow-up (ITT analysis). Deep infections were definite in 252 patients (76%) and suspected in 79 patients (24%). Most of these (84%) were diagnosed within 1 week of randomization (Table 2). A new deep infection after the first week was found in 33 patients (17%) in the levofloxacin group and in 31 patients (16%) in the standard treatment group ($P = 0.80$). The infection focus was treated with drainage or surgery in 224 patients (59%) with no significant difference between the groups.

Endocarditis was observed in 70 patients (18%) with no significant difference between the study groups (Table 2). Endocarditis was classified as definite in 55 patients (79%) and possible in 15 patients (21%). During the follow-up, five patients (1%) had a new SAB more than 28 days after randomization with no significant difference between the groups. Recurrent SAB was due to a relapse in three patients and reinfection in two patients.

Outcome

No significant differences were observed between the treatment groups in ITT or in PP analyses (Table 3). The case fatality rate at 28 days was 14% in both study arms, and at 3 months 21% in the standard treatment and 18% in the levofloxacin group (ITT analysis) (Table 3, Fig. 2).

In patients with a deep infection, case fatality rate at 3 months was significantly higher amongst those who did not receive rifampicin [25 (38%) of 66 patients] than in patients treated with rifampicin [44 (17%) of 265 patients] ($P < 0.001$, OR = 3.06, 95% CI = 1.69–5.54) (Table 4). However, patients who did not receive rifampicin were significantly older and significantly more often had chronic renal failure, a fatal underlying disease, hospital-acquired SAB, or levofloxacin treatment than did those given rifampicin. In contrast, patients not treated with rifampicin had fewer cases of endocarditis and fewer deep infections per patient.

Mortality in patients who had a deep infection was analysed separately amongst those treated with or without rifampicin (stratified CMH test). This was done as the patients in the standard treatment group were treated with rifampicin significantly more often than the patients in the levofloxacin group ($P = 0.003$) (Table 4). The case fatality rate at 3 months amongst patients with deep infection and rifampicin treatment was 13% (15 of 119 patients) in the levofloxacin group and 20% (29 of 146 patients) in the standard treatment group. Case fatality rates in patients not treated with rifampicin were 37% (16 of 43 patients) and 39% (9 of 23 patients). However, the benefit of levofloxacin was not statistically significant in this stratified analysis either, in which the imbalance in the use of rifampicin was taken into account ($P = 0.16$).

The mean duration of fever (>37.5 °C) was 9 days in both groups (Fig. 2). Decrease rates in serum CRP concentration were similar in both groups (Fig. 2). No significant differences were observed between the treatment groups in the number of patients with leucocytosis, leucopenia, thrombocytopenia, acidosis or liver enzyme elevations (data not shown). There were no significant differences in antibiotic-associated diarrhoea caused by *Clostridium difficile* or allergic reactions between the groups.

Discussion

This is the first clinical trial to evaluate the efficacy of a new fluoroquinolone, with improved Gram-positive activity, combined with standard treatment in SAB. In experimental studies, fluoroquinolone combined with standard therapy has shown improvement in treatment results [26] which could not be confirmed in this clinical trial. New treatment options for bacteraemia caused by MRSA strains would be needed. If fluoroquinolones could be useful in MRSA, bacteraemias cannot be answered by this trial because they were not included. However, resistance to fluoroquinolones has been increasing, especially amongst MRSA strains [38].

Overall, 14% of patients in our trial died within 1 month. This is comparable with the mortality of 17% at 28 days we observed in a nationwide, population-based survey of SAB during 1995–2001 in Finland [39], but clearly lower than the overall mortality of 23–39% generally related to

Table 2 Infection foci of 381 patients with *Staphylococcus aureus* bacteraemia randomized either to standard treatment or combined with levofloxacin

	From randomization to 1 week					From 1 week to 3 months				
Infection focus	Levofloxacin group ($n = 191$)	Standard treatment group ($n = 190$)	Total ($n = 381$)	OR (95% CI)	P	Levofloxacin group ($n = 191$)	Standard treatment group ($n = 190$)	Total ($n = 381$)	OR (95% CI)	P
Skin or soft tissue	113 (59)	131 (69)	244 (64)	1.53 (1.01–2.34)	0.05	7 (4)	3 (2)	10 (3)	0.42 (0.11–1.66)	0.20
Central intravenous catheter	23 (12)	15 (8)	38 (10)	0.63 (0.32–1.24)	0.18	0 (0)	0 (0)	0 (0)	–	–
Deep-seated abscess	76 (40)	75 (40)	151 (40)	0.99 (0.66–1.49)	0.95	4 (2)	14 (7)	18 (5)	3.72 (1.20–11.51)	0.02
Intramuscular	24 (13)	27 (14)	51 (13)	1.15 (0.64–2.08)	0.64	1 (1)	6 (3)	7 (2)	6.20 (0.74–51.96)	0.06
Epidural or CNS	23 (12)	15 (8)	38 (10)	0.63 (0.32–1.24)	0.18	3 (2)	6 (3)	9 (2)	2.04 (0.50–8.29)	0.31
Other[a]	45 (24)	42 (22)	87 (23)	0.92 (0.57–1.49)	0.74	5 (3)	7 (4)	12 (3)	1.42 (0.44–4.57)	0.55
Pneumonia	65 (34)	66 (35)	131 (34)	1.93 (0.68–1.58)	0.89	12 (6)	9 (5)	21 (6)	0.74 (0.31–1.80)	0.51
Osteomyelitis	54 (28)	66 (32)	116 (30)	1.23 (0.79–1.90)	0.36	9 (5)	5 (3)	14 (4)	0.55 (0.18–1.66)	0.28
Prosthetic device[b]	28 (15)	40 (21)	68 (18)	1.55 (0.91–2.64)	0.10	2 (1)	0 (0)	2 (1)	–	–
Endocarditis[c]	30 (16)	37 (20)	67 (18)	1.30 (0.76–2.21)	0.33	1 (1)	2 (1)	3 (1)	–	–
Septic arthritis	18 (9)	28 (15)	46 (12)	1.66 (0.89–3.12)	0.11	2 (1)	2 (1)	4 (1)	–	–
Urinary tract	12 (6)	16 (8)	28 (7)	1.38 (0.63–2.98)	0.42	0 (0)	0 (0)	0 (0)	–	–
Mediastinitis	10 (5)	11 (6)	21 (6)	1.11 (0.46–2.68)	0.81	0 (0)	0 (0)	0 (0)	–	–
Deep infection[d]	155 (81)	166 (87)	321 (84)	1.61 (0.92–2.82)	0.10	33 (17)	31 (16)	64 (17)	0.93 (0.55–1.60)	0.80

Values are expressed as n (%), unless otherwise stated. CNS, central nervous system. [a]Patients with parenchymal, lung, peritoneal, subphrenic, gynaecological and pericardial abscesses, or pleural empyema. [b]Patients with orthopedic, cardiac valve and intravascular devices without peripheral or central intravenous catheters. [c]Possible or definite endocarditis by modified Duke criteria. [d]Patients with deep-seated abscess, pneumonia, osteomyelitis, infection of prosthetic device, endocarditis, septic arthritis, urinary tract infection, mediastinitis, meningitis, septic thrombophlebitis and recurrent *S. aureus* bacteraemia. Each patient has been included once, although some patients had several deep infections at various time-points.

Table 3 Outcome in various subgroups at 28 days and at 3 months for 381 patients with *Staphylococcus aureus* bacteraemia

	At 28 days					At 3 months				
Case fatality rate	Levofloxacin group	Standard treatment group	Total	OR (95% CI)	*P*	Levofloxacin group	Standard treatment group	Total	OR (95% CI)	*P*
Deaths, all	26/191 (14)	27/190 (14)	53/381 (14)	1.05 (0.59–1.88)	0.87	34/191 (18)	39/190 (21)	73/381 (19)	1.19 (0.72–1.99)	0.50
Age										
≤65 years	9/110 (8)	9/113 (8)	18/223 (8)	0.97 (0.37–2.55)	0.95	12/110 (11)	14/113 (12)	26/223 (12)	1.15 (0.51–2.62)	0.73
>65 years	17/81 (21)	18/77 (23)	35/158 (22)	1.15 (0.54–3.67)	0.72	22/81 (27)	25/77 (33)	47/158 (30)	1.29 (0.65–2.55)	0.47
Community-acquired	9/89 (10)	12/85 (14)	21/174 (12)	1.46 (0.58–3.67)	0.42	10/89 (11)	15/85 (18)	25/174 (14)	1.69 (0.71–4.01)	0.23
Hospital-acquired	17/102 (17)	15/105 (14)	32/207 (16)	0.83 (0.39–1.77)	0.64	24/102 (24)	24/105 (23)	48/207 (23)	0.93 (0.50–1.84)	0.91
Diabetes	6/50 (12)	7/53 (13)	13/103 (13)	1.12 (0.35–3.58)	0.85	9/50 (18)	13/53 (25)	22/103 (21)	1.48 (0.57–3.85)	0.42
McCabe's classification										
Healthy or nonfatal	10/134 (8)	12/134 (9)	22/268 (8)	1.22 (0.51–2.93)	0.66	11/134 (8)	18/134 (13)	29/268 (11)	1.74 (0.79–3.83)	0.17
Ultimately or rapidly fatal	16/57 (28)	15/56 (27)	31/113 (27)	0.94 (0.41–2.14)	0.88	23/57 (40)	21/56 (38)	44/113 (39)	0.89 (0.42–1.89)	0.76
Central intravenous catheter	4/23 (17)	1/15 (7)	5/38 (13)	0.34 (0.03–3.38)	0.34	5/23 (22)	2/15 (13)	7/38 (18)	0.55 (0.09–3.31)	0.51
Endocarditis[a]	8/31 (26)	9/39 (23)	17/70 (24)	0.86 (0.29–2.58)	0.79	10/31 (32)	13/39 (33)	23/70 (33)	1.05 (0.38–2.87)	0.92
Deep infection[b]	24/158 (15)	27/168 (16)	51/326 (16)	0.94 (0.51–1.70)	0.83	31/162 (19)	38/169 (23)	69/331 (21)	0.82 (0.48–1.39)	0.45

Values are expressed as *n*/*N* (%), unless otherwise stated. [a]Possible or definite endocarditis by modified Duke criteria. [b]Patients with deep-seated abscess, pneumonia, osteomyelitis, infection of prosthetic device, endocarditis, septic arthritis, urinary tract infection, mediastinitis, meningitis, septic thrombophlebitis and recurrent *S. aureus* bacteraemia.

Fig. 2 Kaplan–Meier estimates of the overall survival (panel a) and mean time to defervescence (panel b), and decrease of C-reactive protein concentration (mean ± SD) (panel c) in 381 patients with *Staphylococcus aureus* bacteraemia treated with standard treatment ($n = 190$) or combined with levofloxacin ($n = 191$).

Table 4 *Post hoc* analysis of the characteristics and outcome at 3 months of patients with deep infection who received a combination therapy with or without rifampicin

Outcome and variable	Rifampicin ($n = 265$)	No rifampicin ($n = 66$)	Total ($n = 331$)	OR (95% CI)	*P*
Case fatality rate at 3 months	44 (17)	25 (38)	69 (21)	3.06 (1.69–5.54)	<0.001
Age (mean years ± SD)	57 ± 18	64 ± 19	58 ± 18	–	0.006
Male sex	174 (66)	37 (56)	211 (64)	1.50 (0.87–2.60)	0.15
Hospital-acquired	128 (48)	44 (67)	172 (52)	0.47 (0.27–0.82)	0.008
Diabetes	70 (26)	15 (23)	85 (26)	1.22 (0.65–2.31)	0.54
Chronic renal failure	30 (11)	15 (23)	45 (14)	0.43 (0.22–0.87)	0.02
Hepatic cirrhosis	38 (14)	14 (21)	52 (16)	0.62 (0.31–1.23)	0.17
Cancer	30 (11)	8 (12)	38 (12)	0.93 (0.40–2.13)	0.86
Haematological malignancy	8 (3)	4 (6)	12 (4)	0.48 (0.14–1.65)	0.24
McCabe's classification					
Healthy or nonfatal	199 (75)	36 (55)	235 (71)	1.00 Ref.	–
Ultimately or rapidly fatal	66 (25)	30 (46)	96 (29)	0.40 (0.23–0.70)	<0.001
Central intravenous catheter	16 (6)	6 (9)	22 (7)	0.64 (0.24–1.71)	0.37
Endocarditis[a]	62 (23)	8 (12)	70 (21)	2.21 (1.00–4.89)	0.04
Corticosteroids[b]	106 (40)	21 (32)	127 (38)	1.43 (0.81–2.53)	0.22
Number of deep infections per patient					
≤2	151 (57)	53 (80)	204 (62)	1.00 Ref.	–
>2	114 (43)	13 (20)	127 (38)	3.08 (1.60–5.92)	<0.001
Initial therapy at randomization					
Cloxacillin or dicloxacillin	207 (78)	48 (73)	255 (77)	1.34 (0.72–2.48)	0.35
Cefuroxime	42 (16)	14 (21)	56 (17)	0.70 (0.36–1.38)	0.30
Vancomycin	35 (13)	5 (8)	40 (12)	1.86 (0.70–4.94)	0.21
Levofloxacin	119 (45)	43 (65)	162 (49)	2.29 (1.31–4.02)	0.003

Values are expressed as *n* (%), unless otherwise stated. [a]Possible or definite endocarditis by modified Duke criteria. [b]During 3 months after randomization.

SAB [1, 6]. Direct comparison of SAB mortality with previous studies is complicated by inconsistent definitions and variable analysis time-points. In some studies only mortality directly attributable to SAB has been calculated [1, 9, 40]. Recent nationwide surveys from low resistance areas in Finland and Denmark [39, 41] suggest that mortality in SAB has decreased during the recent decade, which might be one explanation for the lower mortality in this trial when compared with previous studies.

In the present trial, all patients were followed by an infectious disease specialist, which has been shown to improve the outcome and reduce the number of relapses [6, 42]. However, the low mortality in this trial is in contrast to the high prevalence of deep infections which has earlier been related to higher mortality [6, 9]. The reported frequency of deep infections has varied from 10% to 50%, but it was over 80% in the present trial [9, 13–16]. This difference might be partly explained by different definitions as well as by the high intensity search for deep infections in our trial. Furthermore, in most articles, the incidence of deep infections has not been separately reported or they have been classified into primary and metastatic foci. In another recent study [9], 74% of complications were already present at the time of hospitalization, in accordance with our findings of most deep infections being evident during the first week. These data suggest that infection foci cannot be reliably classed as primary or metastatic and that identification of deep infections might be essential for decreased mortality in SAB.

Intravenous antibiotic treatment is recommended for 4–6 weeks in SAB with a deep infection [17, 43]. In this trial, the duration of parenteral and oral antibiotic therapy was much more prolonged and extended with an average of 77 days. Of all patients, 44% remained on antibiotic treatment at 3 months. This may have contributed to the low (1%) prevalence of SAB recurrences. Significantly higher recurrence rates from 9% to 23%, have been reported in studies with slightly longer follow-up times from 3 to 6 months [5, 7–10, 42, 44].

Data on the effect and recommendations of various antibiotic combinations are controversial,

although they are widely used in complicated SAB. Rifampicin shows excellent antistaphylococcal activity, penetrating well into cells and killing phagocytosed bacteria [22, 23]. The combination of oxacillin and rifampicin has shown a synergistic action *in vitro* when the concentration ratio of oxacillin to rifampicin was low, whereas antagonism occurred with higher ratios [19]. Some small randomized studies have suggested that adding rifampicin to standard treatment improves clinical cure and bacteriological eradication whereas no effect in mortality has been seen [20, 21, 45]. Furthermore, rifampicin is often used in combination with standard treatment in deep-seated abscesses [18], osteomyelitis [45], foreign body infections and endocarditis, or because of poor response to the standard treatment [12, 22–24].

In the current trial, rifampicin was included in the protocol for all patients with deep infection as the ultimate aim was to evaluate whether levofloxacin improved the treatment results when the best therapy was used. Interestingly, if rifampicin was not given, mortality was significantly higher. However, this result must be interpreted with caution, because the trial was not specifically designed to scrutinize the effect of rifampicin. In addition, patients not receiving rifampicin had factors generally associated with higher mortality [6, 14, 40, 44]. These patients were older, more often had hospital-acquired SAB and ultimately or rapidly fatal diseases.

In the levofloxacin group there were significantly more patients with a deep infection not treated with rifampicin (27%) when compared with the standard treatment group (14%). The reasons for not using rifampicin were a concomitant liver disease in 15 cases (nine patients in the levofloxacin group versus six patients in the standard treatment group), a risk of a drug interaction or other decision of the treating doctor in 47 cases (31 patients versus 16 patients), and an early death of the patients in four cases (3 patients versus 1 patient). In patients with deep infection receiving rifampicin, a trend for lower mortality (13%) was observed in the levofloxacin group when compared with the standard treatment group (20%). This difference, however, was not statistically significant. As the present study design did not directly compare levofloxacin to rifampicin, the potential benefit of levofloxacin when rifampicin cannot be used remains to be shown in further prospective studies.

In summary, levofloxacin in combination with standard treatment in SAB did not decrease the mortality or the incidence of deep infections, nor did it speed up recovery. The data indicate that a fluoroquinolone could not be recommended to be combined with the standard treatment of SAB. However, patients with a deep infection appeared to benefit from combination treatment including rifampicin, as suggested also by experimental data.

Conflict of interest statements

Eeva Ruotsalainen has occasionally consulted Aventis Pharma. Asko Järvinen and Ville Valtonen have occasionally consulted several companies, including Aventis Pharma, Bayer, Pfizer, AstraZeneca, Roche, Pharmacia and Merck & Co., Inc. Irma Koivula has occasionally consulted Aventis Pharma and Orion Pharma. Jukka Lumio has occasionally consulted AstraZeneca, Bayer, Pfizer, and Aventis Pharma. Heikki Kauma, Esa Rintala, Pirkko Kotilainen, Martti Vaara, and Jukka Nikoskelainen have no conflicts of interest to declare.

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