Subphenotype- and complication-guided adjunctive fosfomycin versus standard monotherapy in *Staphylococcus aureus* bacteraemia: pooled analysis of two randomised trials

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Summary

Background **Randomised trials of combination therapies for *S. aureus* bacteraemia (SAB) have failed to improve clinical outcomes—likely reflecting the lack of risk-targeted patient selection. The FEN-AUREUS classification enables early risk stratification based on clinical subphenotypes. We aimed to validate this framework in a pooled trial cohort and assess whether combining subphenotypes with IDSA-defined complicated SAB could identify patients most likely to benefit from adjunctive fosfomycin.**

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Methods We conducted a post-hoc analysis of individual-level data from two multicentre randomised trials evaluating adjunctive fosfomycin in SAB. Participants were classified according to the FEN-AUREUS framework into phenotypes and risk subphenotypes. Associations between subphenotype, complicated bacteraemia, and 60-day mortality as the primary outcome and 30-day mortality and 8-week treatment success as secondary outcomes were assessed. A DOOR analysis provided an integrated assessment of overall outcomes. This study is registered with ClinicalTrials.gov, NCT07155590.

Findings Among 369 patients (median age 68 years, IQR 56–78; 262/369 [68·8%] male), high-risk subphenotypes were associated with greater 60-day mortality (23·2% versus 6·6%; risk ratio [RR] 3·49, 95% confidence interval [CI] 1·87–6·52; adjusted hazard ratio [aHR] 3·38, 1·69–6·78), regardless of complication status. Combining risk subphenotypes with the IDSA classification showed heterogeneity in response to adjunctive fosfomycin. In patients with low-risk and uncomplicated SAB (n = 107), 60-day mortality was low with both monotherapy and adjunctive fosfomycin (2·1% versus 3·4%; risk difference [RD] −1·3% [95% CI −7·4 to 4·8]; p = 0·68), and treatment success at week 8 exceeded 89%. In the intermediate strata, 60-day mortality was 18·8% with monotherapy versus 7·4% (RD 11·3% [95% CI −5·4 to 28·1]; p = 0·20) with adjunctive fosfomycin in low-risk/complicated SAB (n = 59), and 15·0% versus 22·8% (RD −7·8% [95% CI −19·9 to 4·3]; p = 0·21) in high-risk/uncomplicated SAB (n = 159); week-8 treatment success was 78·1% versus 88·9% and 61·3% versus 54·4%, respectively. By contrast, in high-risk, complicated SAB (n = 44), adjunctive fosfomycin was associated with higher treatment success (25·8% versus 69·2%; RD −43·4% [−72·9 to −14·0]; p = 0·007) and a non-significant reduction in 60-day mortality (45·2% versus 23·1%). DOOR analysis suggested a more favourable overall outcome profile with adjunctive therapy in this subgroup.

Interpretation Integrating early risk subphenotyping with IDSA complication criteria may enable more precise identification of SAB patients who may benefit from intensified therapy, while supporting monotherapy in those at lowest risk. This stratified approach provides a practical framework to refine patient selection for future trials and personalised therapeutic strategies.

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Keywords: *Staphylococcus aureus* bacteraemia; Risk stratification; Clinical phenotypes; Subphenotypes; Monotherapy; Adjunctive therapy; Fosfomycin; Complicated bacteraemia; Randomised controlled trial

Introduction

Staphylococcus aureus bacteraemia (SAB) remains a major global cause of bloodstream infection and sepsis-related mortality, with 30-day case fatality rates ranging 15% and 30% depending on host status, infection source, and associated complications.[1–3] This wide variability, together with significant heterogeneity in diagnostic and therapeutic approaches across settings, highlights the complex and multifaceted nature of SAB.[4,5]

Traditionally, the clinical management of SAB has differentiated between uncomplicated and complicated cases, according to the presence of risk factors for metastatic complications or poor outcomes, as outlined in the Infectious Diseases Society of America (IDSA) guidelines.[6] However, this dichotomous framework has been increasingly questioned, and focuses more on predicting complications than on mortality risk.[7–10]

Recent work has introduced an alternative framework for early clinical risk stratification based on the identification of clinical subphenotypes. The FEN-AUREUS project, in particular, developed a phenotyping algorithm that incorporates portal of entry (source phenotype) and readily available clinical variables within the first 24 h of SAB onset, deriving risk subphenotypes that were internally validated in two large observational cohorts.[11] These subphenotypes were strongly associated with 30-day mortality and showed potential utility for guiding early therapeutic decision-making and diagnostic intensity. Importantly, this approach may complement current definitions of complicated SAB by capturing early indicators of host vulnerability and disease severity.

To date, randomised controlled trials (RCTs) evaluating adjunctive antibiotic therapy in SAB—including rifampicin, gentamicin, ceftaroline or other β-lactams, and fosfomycin—have largely been unable to demonstrate consistent benefits in clinical outcomes, and have raised concerns about increased toxicity.[12–18] This experience underscores the limitations of a uniform treatment approach and highlights the need for risk-guided, personalised SAB management. While the inclusion of

Research in context

Evidence before this study

We searched PubMed, Scopus, and ClinicalTrials.gov from January 1, 2000, to September 1, 2025, using the terms "*Staphylococcus aureus* bacteraemia" OR "*S. aureus*" AND ("adjunctive therapy" OR "combination therapy" OR "fosfomycin") AND ("phenotype" OR "subphenotype" OR "risk stratification" OR "complicated bacteraemia" OR "severity"). We selected observational studies and randomised controlled trials published in English. We found that existing trials evaluating adjunctive antibiotics in SAB have been unable to demonstrate consistent benefit in unselected populations, raising concerns about toxicity and absence impact on mortality, thereby underscoring the need to move towards personalised approaches to its management. A recent multicentre study (FEN-AUREUS) developed a phenotyping tool that allows clinicians to stratify SAB patients early by risk of mortality, using readily available clinical and laboratory data within 24 h. However, this tool had been previously validated only in observational cohorts, and no studies had applied it to randomised trial populations or assessed its integration with conventional definitions of complicated SAB to better predict treatment response.

Added value of this study

This is the first study to externally validate the FEN-AUREUS classification using individual participant data from two randomised controlled trials. We confirmed that early clinical subphenotypes are independent predictors of mortality. By combining FEN-AUREUS risk subphenotypes with IDSA-defined criteria for complicated SAB, we identified a subgroup of patients at particularly high-risk, in whom adjunctive fosfomycin use was associated with improved treatment success. By contrast, patients with low-risk and uncomplicated profiles achieved similarly favourable outcomes with monotherapy as with intravenous fosfomycin combination therapy. We also identified two intermediate groups (low-risk/complicated and high-risk/uncomplicated) with heterogeneous response to intravenous fosfomycin.

Implications of all the available evidence

Integrating early phenotyping with conventional criteria for complicated SAB provides a practical bedside approach to guide personalised treatment, identifying patients most likely to benefit from adjunctive fosfomycin therapy, while supporting safe monotherapy use in a substantial proportion of patients. This approach may further contribute to improving the design and interpretation of future randomised controlled trials in SAB by reducing heterogeneity and allowing more accurate estimates of treatment effect.

large proportions of low-risk, uncomplicated cases in prior trials likely obscured potential benefits, patients at higher predicted risk of mortality or with indicators of poor response—such as persistent bacteraemia or metastatic complications—may represent the most appropriate candidates for combination therapy.

In this context, combining risk subphenotyping with established definitions of complicated SAB offers a novel strategy to identify patient subgroups most likely to benefit from intensified or adjunctive antibiotic regimens. Such an approach could also help refine the design and interpretation of future RCTs in SAB, by reducing heterogeneity and enabling more precise estimates of treatment effect.[19]

This study aimed to externally validate the prognostic value of FEN-AUREUS risk subphenotypes in a pooled cohort of SAB patients from two RCTs evaluating adjunctive fosfomycin,[20,21] to examine whether integrating the IDSA definition of complicated versus uncomplicated bacteraemia with the FEN-AUREUS risk subphenotypes enables stratification into groups with different risks of death, and to assess the effectiveness of adjunctive fosfomycin compared with standard monotherapy within these risk groups. We hypothesised that adjunctive fosfomycin would provide the greatest benefit in patients with high-risk subphenotypes and complicated infection, while offering limited benefit in those with low-risk subphenotypes and uncomplicated disease.

Methods

Study design and population

We conducted a post-hoc analysis of the BACSAFO cohort, which pooled individual participant data from two multicentre, randomised, superiority trials evaluating adjunctive fosfomycin versus standard monotherapy for the treatment of SAB: BACSARM and SAFO.[20,21] Common inclusion criteria for both trials were age ≥18 years and at least one blood culture positive for MRSA or MSSA within 72 h before enrolment, with evidence of active infection. Patients with uncomplicated or complicated SAB were eligible. Exclusion criteria included polymicrobial bacteraemia, allergy to study drugs, severe liver disease (Child-Pugh C), prosthetic valve endocarditis, pregnancy, expected survival <24 h, or concurrent participation in another clinical trial. Additional exclusions were MRSA pneumonia in the BACSARM trial (due to daptomycin limitations in pneumonia) and acute SARS-CoV-2 infection in the SAFO trial. Patient selection and inclusion in the pooled post-hoc analysis are summarised in Supplementary Figure S1.

In the BACSARM trial,[20] 155 patients were randomised across 18 Spanish hospitals to receive daptomycin (10 mg/kg per day) plus intravenous fosfomycin sodium (2 g every 6 h) or daptomycin alone. Daptomycin was infused over 30 min and fosfomycin over 60 min. Treatment lasted 10–14 days for uncomplicated SAB and 28–42 days for complicated SAB or when an endovascular device other than an intravascular catheter was present. Fosfomycin was co-administered with daptomycin throughout treatment.

In the SAFO trial,[21] 214 patients were randomised in 19 Spanish hospitals to receive cloxacillin (2 g every 4 h) plus intravenous fosfomycin sodium (3 g every 6 h; infused over 4 h) or cloxacillin alone. Combination therapy was given for the first 7 days. Both trials included renal function–adjusted dosing. In SAFO, clinicians were advised to administer potassium supplementation and furosemide to prevent sodium overload in patients receiving fosfomycin.

The present study included all patients in the modified intention-to-treat (mITT) populations of both RCTs, defined as all randomised patients who received at least one day of antibiotic therapy (referred to as mITT in BACSARM and ITT in SAFO). Patients receiving any treatment regimen that included fosfomycin were classified into the adjunctive fosfomycin group, while those treated without fosfomycin were assigned to the monotherapy group. The study was approved by the Bellvitge University Hospital Ethics Committee (EOMO33/24). Informed consent was obtained during the BACSARM and SAFO trials. This analysis was reported according to CONSORT recommendations (Supplementary Table S1).

Variables and definitions

All clinical, laboratory, and outcome variables were prospectively collected within the BACSARM and SAFO trials, as previously described,[18] with proxy data required for five in fewer than 10% of cases (Supplementary Table S2).

Source phenotypes and risk subphenotypes were assigned using the publicly available FEN-AUREUS online calculator (https://fen-aureus.com). This tool first assigns patients to a source phenotype based on the probable portal of entry (A: skin or soft tissue; B: catheter-related; C: unknown or other). Subsequently, risk subphenotypes (1 = low risk; 2 = high risk) are derived from early clinical variables and logistic regression modelling. Patients with a calculated probability $\geq$50% were assigned to subphenotype 2.

We defined complicated SAB according to IDSA guidelines as the presence of any of the following: endocarditis, prosthetic material, persistent positive blood cultures at $\geq$72 h, metastatic complications, or persistent fever at 72 h.[6] Although IDSA complication status was not a pre-specified stratification factor in the original trial protocols, all relevant variables were prospectively collected.

The primary outcome of this study was all-cause mortality at 60 days after randomisation. Secondary outcomes included all-cause mortality at 30 days and treatment success at 8 weeks after randomisation, defined as survival without clinical relapse and resolution of symptoms. Treatment success was included as a secondary outcome to evaluate the effectiveness of adjunctive fosfomycin within stratified subgroups. To comprehensively assess clinical benefit and safety, we also performed a Desirability of Outcome Ranking (DOOR) analysis.[22]

Statistical analysis

We used descriptive statistics to summarise baseline characteristics by treatment group and phenotype. Categorical variables were reported as n/N (%) and continuous variables as median [IQR]; between-group imbalance was summarised using standardised mean differences (SMDs). Associations between clinical subphenotype and complicated bacteraemia (as defined by IDSA criteria) with study 60- and 30-day mortality were assessed using effect-size measures. Crude risk ratios (RRs) with 95% confidence intervals were calculated for binary outcomes.

For time-to-event outcomes, adjusted hazard ratios (aHRs) were obtained from Cox proportional hazards models, which included centre effect, the presence of complicated bacteraemia, and risk subphenotype classification as covariates. To account for the 'centre effect' without introducing model instability due to the large number of participating hospitals, we did not include each centre as an individual variable. Instead, we used a TreeNet (Salford Systems) gradient boosting analysis to classify centres based on their mortality risk, adjusted for patient severity, comorbidities, management variables, and other clinical covariates. Hospitals were subsequently grouped into a binary covariate ('high-risk centre' versus 'low-risk centre'), which was included in the multivariable Cox regression models.

We defined risk subphenotype as low-risk (A1, B1, C1) or high-risk (A2, B2, C2) according to the FEN-AUREUS tool.

For comparing adjunctive fosfomycin versus standard monotherapy within pre-specified strata, treatment effects were expressed as absolute risk differences (RDs) with 95% CIs, defined as monotherapy – adjunctive. Under this convention, a positive RD favours adjunctive therapy for mortality endpoint, whereas a negative RD favours adjunctive therapy for treatment-success endpoint.

Additionally, we performed a DOOR analysis to integrate treatment success at week 8, adverse events leading to treatment discontinuation, and 60-day mortality into a single ordinal endpoint, comparing

monotherapy with adjunctive fosfomycin. The DOOR categories were defined as follows: (1) treatment success at week 8 without adverse events; (2) treatment success at week 8 with adverse events; (3) no treatment success at week 8 and survival at day 60; and (4) mortality at day 60.

We performed all analyses using SPSS version 26·0 (IBM Corp., Armonk, NY), and TreeNet (Salford Systems). The study is registered with ClinicalTrials.gov, NCT07155590.

Role of the funding source

The funder of the study (Instituto de Salud Carlos III) had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Validation of risk subphenotypes in the BACSAFO cohort

A total of 369 patients with SAB were included in the pooled BACSAFO cohort (Supplementary Figure S2). The median age was 68 years (IQR 56–78), 68·8% were male, and the median Charlson age-adjusted index was 4 (IQR 2–6). The all-cause 60-day mortality was 15·7% (58/369), while 30-day mortality was 11·4% (42/369). Patients who died by day 60 were older (SMD = 0·99; RR per 1-SD increase in age = 2·72, 95% CI 1·94–3·80), and more likely to have solid tumours (RR = 2·03, 1·26–3·28) or dementia (RR = 2·93, 1·52–5·63). They also showed higher neutrophil counts (RR per 1-SD = 1·35, 1·16–1·57), lower oxygen saturation (RR per 1-SD = 0·74, 0·64–0·86), and reduced Glasgow Coma Scale scores (RR per 1-SD = 0·83, 0·72–0·95) at the time of bacteraemia (Supplementary Table S3).

Based on the portal of entry, 88 patients (23·8%) were classified as phenotype A (skin and soft tissue), 154 patients (41·7%) as phenotype B (vascular device-associated), and 127 patients (34·4%) as phenotype C (other portals of entry or unknown). There were marked imbalances in age and comorbidities within phenotypes (Table 1). This was consistent with a worse clinical profile in the high-risk subphenotypes (A2, B2, C2), as shown in the 60-day Kaplan–Meier curves presented in Fig. 1 (A, B and C).

Overall, 166 patients (45·0%) were assigned to low-risk subphenotype 1 (A1, B1, C1), and 203 (55·0%) to high-risk subphenotype 2 (A2, B2, C2). In a sensitivity analysis excluding variables with missing data, the distribution of patients and mortality across risk groups was similar to that observed when all cases were included using proxy values.

Patients in high-risk subphenotype 2 had significantly higher 60-day mortality compared to those in low-risk subphenotype 1 (23·2% versus 6·6%, RR = 3·49, 95% CI 1·87–6·52) (Table 2 and Fig. 1D, log-rank test $p < 0·0001$). These associations remained consistent in multivariable analysis adjusting for complicated bacteraemia and centre effects (aHR for 60-day mortality: 3·38, 95% CI 1·69–6·78, p = 0·0001; aHR for 30-day mortality: 2·84, 95% CI 1·30–6·23, p = 0·009) (Supplementary Table S4).

Integration of FEN-AUREUS subphenotypes and IDSA complicated bacteraemia criteria for mortality risk stratification

When aggregated FEN-AUREUS risk subphenotypes were combined with the IDSA definition of complicated bacteraemia, a clear 60-day mortality gradient emerged across the four resulting strata (Table 2), as further illustrated by the Kaplan–Meier curves (log-rank test $p < 0·001$; Fig. 2). Patients classified with a low-risk subphenotype and uncomplicated SAB experienced the most favourable outcomes, with mortality rates of only 2·8% at both 30 and 60 days. In contrast, the group with a high-risk subphenotype and complicated infection showed the poorest survival, with 60-day mortality reaching 38·6% (RR = 13·78 [95% CI: 4·25–44·67]; $p < 0·0001$).

Effectiveness of adjunctive fosfomycin versus standard monotherapy within stratified subgroups

In the subgroup of patients with uncomplicated and low-risk bacteraemia (N = 107), 60-day mortality was very low and similar between those receiving monotherapy (2·1%) and those treated with adjunctive fosfomycin (3·4%); the absolute difference (monotherapy—adjunctive) was –1·3% ([95% CI –7·4 to 4·8]; p = 0·68, Table 3 and Supplementary Figures S3A and S4A). Treatment success at 8 weeks after randomisation was 89·6% with monotherapy and 89·8% with adjunctive fosfomycin; absolute risk difference (monotherapy—adjunctive): –0·2% (95% CI –11·8 to 11·3; p = 0·97; Table 3, Supplementary Figure S3B). In this subgroup, the estimated number needed to treat (NNT) was 77 for 60-day mortality and 500 for treatment success at week 8.

Outcomes in the intermediate-risk strata were heterogeneous (Table 3). In low-risk but complicated SAB (N = 59), 60-day mortality was numerically lower with adjunctive fosfomycin (7·4% versus 18·8%), whereas in high-risk but uncomplicated SAB (N = 159) mortality was numerically higher (22·8% versus 15·0%); however, neither difference reached statistical significance.

In the highest-risk subgroup, with complicated bacteraemia and high-risk subphenotype (N = 44), outcomes were notably worse. The 60-day mortality was 45·2% and 23·1% with adjunctive fosfomycin; the absolute difference (monotherapy—adjunctive) was +22·1% (95% CI –6·8 to 50·9; p = 0·17, Supplementary Figures S3B and S4A). Treatment success at 8 weeks was significantly higher with adjunctive fosfomycin (69·2%) compared to monotherapy (25·8%)

Variable	All (N = 369)	Phenotype A (N = 88)			Phenotype B (N = 154)			Phenotype C (N = 127)		
		A1 (N = 42)	A2 (N = 46)	SMD A	B1 (N = 77)	B2 (N = 77)	SMD B	C1 (N = 47)	C2 (N = 80)	SMD C
Demographics										
Male sex, n (%)	262 (68·8)	30 (71·4)	31 (67·4)	−0·09	53 (68·8)	52 (67·5)	−0·028	33 (70·2)	55 (68·8)	−0·032
Age, median [IQR] (years)	68 (56–78)	64 (55–73)	73 (62–78)	0·42	65 (52–72)	70 (57–80)	0·31	64 (54–73)	76 (62–82)	0·65
Comorbidities										
DM uncomplicated, n (%)	76 (20·6)	8 (19·0)	6 (13·0)	−0·16	16 (20·8)	14 (18·2)	−0·066	6 (12·8)	26 (32·5)	0·45
DM end–stage organ disease, n (%)	58 (15·7)	11 (26·2)	14 (30·4)	0·09	7 (9·1)	15 (19·5)	0·30	4 (8·5)	7 (8·8)	0·009
Any solid tumour, n (%)	76 (20·6)	8 (19·0)	9 (19·6)	0·01	14 (18·2)	15 (19·5)	0·033	9 (19·1)	21 (26·3)	0·17
Chronic kidney disease, n (%)	72 (19·6)	0 (0·0)	17 (37·0)	0·94	9 (11·7)	28 (36·4)	0·58	1 (2·1)	17 (21·3)	0·55
Peripheral vasculopathy, n (%)	68 (18·4)	8 (19·0)	23 (50·0)	0·65	7 (9·1)	15 (19·5)	0·30	7 (14·9)	8 (10·0)	0·13
Chronic obstructive pulmonary disease n (%)	55 (14·9)	4 (9·5)	5 (10·9)	0·04	7 (9·1)	16 (20·8)	0·33	5 (10·6)	18 (22·5)	0·50
Ischemic cardiopathy, n (%)	47 (12·7)	11 (26·2)	5 (10·9)	−0·40	12 (15·6)	9 (11·7)	−0·11	3 (6·4)	7 (8·8)	0·088
Congestive heart failure, n (%)	43 (11·7)	5 (11·9)	8 (17·4)	0·16	5 (6·5)	13 (16·9)	0·32	0 (0·0)	12 (15·0)	0·20
Ictus or hemiplegia, n (%)	34 (9·2%)	2 (4·8)	5 (10·9)	0·23	11 (14·3)	11 (14·3)	0·00	1 (2·1)	4 (5·0)	0·15
Liver disease, n (%)	30 (8·2)	1 (2·4)	7 (15·2)	0·45	4 (5·2)	8 (10·4)	0·19	3 (6·4)	7 (8·8)	0·25
Haematologic neoplasm, n (%)	17 (4·6)	0 (0·0)	1 (2·2)	0·21	4 (5·2)	6 (7·8)	0·11	3 (6·4)	3 (3·8)	−0·12
Connective tissue disease, n (%)	15 (4·1%)	2 (4·8)	2 (4·3)	−0·02	2 (2·6)	2 (2·6)	0·00	3 (6·4)	4 (5·0)	−0·061
Dementia, n (%)	14 (3·8)	1 (2·4)	4 (8·7)	0·27	1 (1·3)	3 (3·9)	0·16	2 (4·3)	3 (3·8)	−0·026
Ulcerative disease, n (%)	8 (2·2)	1 (2·4)	2 (4·3)	0·11	1 (1·3)	1 (1·3)	0·00	2 (4·3)	1 (1·3)	−0·20
HIV infection	4 (1·1)	1 (2·4)	0 (0·0)	−0·23	1 (1·3)	2 (2·6)	0·094	0 (0·0)	0 (0·0)	0·000
Age–adjusted Charlson index [IQR] (points)	4 (2–6)	4 (2–7)	4 (2–5)	−0·39	4 (2–6)	3 (2–5)	−0·24	4 (1–5)	4 (2–6)	0·065
Characteristics of SAB										
Complicated bacteraemia,[a] n (%)	103 (27·9)	15 (35·7)	12 (26·1)	−0·21	21 (27·3)	12 (15·6)	−0·29	23 (48·9)	20 (25·0)	−0·51
Nosocomial acquisition, n (%)	154 (41·7)	12 (28·6)	11 (23·9)	−0·11	43 (55·8)	47 (61·0)	0·105	1 (2·1)	40 (50·0)	1·02
Endocarditis at end–of–treatment, n (%)	25 (6·8)	4 (9·5)	4 (8·7)	−0·03	5 (6·5)	5 (6·5)	0·000	2 (4·3)	5 (6·3)	0·087
Inflammatory markers and clinical data at the day of bacteraemia										
Creatinine [IQR] (mg/dL)	1·01 (0·77–1·57)	0·82 (0·69–1·07)	1·42 (1·00–2·74)	0·98	0·92 (0·70–1·47)	1·08 (0·86–1·90)	0·056	0·83 (0·62–1·04)	1·27 (0·88–1·78)	0·64
Neutrophiles [IQR] (10^3 cells/μL)	5·52 (4·30–9·20)	5·69 (4·39–9·20)	7·20 (4·43–13·95)	0·49	4·97 (4·02–6·70)	5·21 (4·09–8·18)	0·26	5·04 (4·20–6·20)	7·57 (5·21–14·07)	0·64
GCS [IQR] (points)	15 (15–15)	15 (15–15)	15 (15–15)	−0·14	15 (15–15)	15 (15–15)	−0·05	15 (15–15)	15 (15–15)	−0·32
SpO2 [IQR] (%)	99 (96–99)	98 (96–99)	99 (95–99)	−0·14	99 (95–99)	99 (96–99)	−0·078	99 (98–99)	98·5 (95–99)	−0·29
Pitt [IQR] (points)	0 (0–1)	0 (0–1)	0 (0–1)	0·15	0 (0–1)	0 (0–2)	0·32	0 (0–1)	0 (0–1)	0·38
30–day mortality	42 (11·4)	1 (2·4)	8 (17·4)	0·49	4 (5·2)	11 (14·3)	0·31	4 (8·5)	14 (17·5)	0·26
60–day mortality	58 (15·7)	1 (2·4)	12 (26·8)	0·67	6 (7·8)	15 (19·5)	0·34	4 (8·5)	20 (25·0)	0·42

Data are n (%) for categorical variables and median [IQR] for continuous variables. Percentages in parentheses are within-column proportions for each subphenotype. IQR = interquartile range (25th–75th percentile). Subphenotypes are shown within three clinical phenotypes (A, B, C); within each phenotype, "1" denotes the lower-risk subphenotype and "2" the higher-risk subphenotype. The SMD (standardised mean difference) columns quantify within-phenotype imbalance as subphenotype 2 minus subphenotype 1: positive SMD indicates higher mean/prevalence in subphenotype 2; negative SMD indicates higher values in subphenotype 1. Magnitude guide for |SMD|: <0·10 negligible, 0·10–0·20 small, 0·20–0·50 moderate, >0·50 large. Abbreviations: DM = diabetes mellitus; GCS = Glasgow Coma Scale; SpO2 = peripheral oxygen saturation. [a]Complicated bacteraemia is defined according to IDSA criteria.

Table 1: **Baseline characteristics of clinical subphenotypes identified in the pooled individual-participant dataset from two randomised trials.**

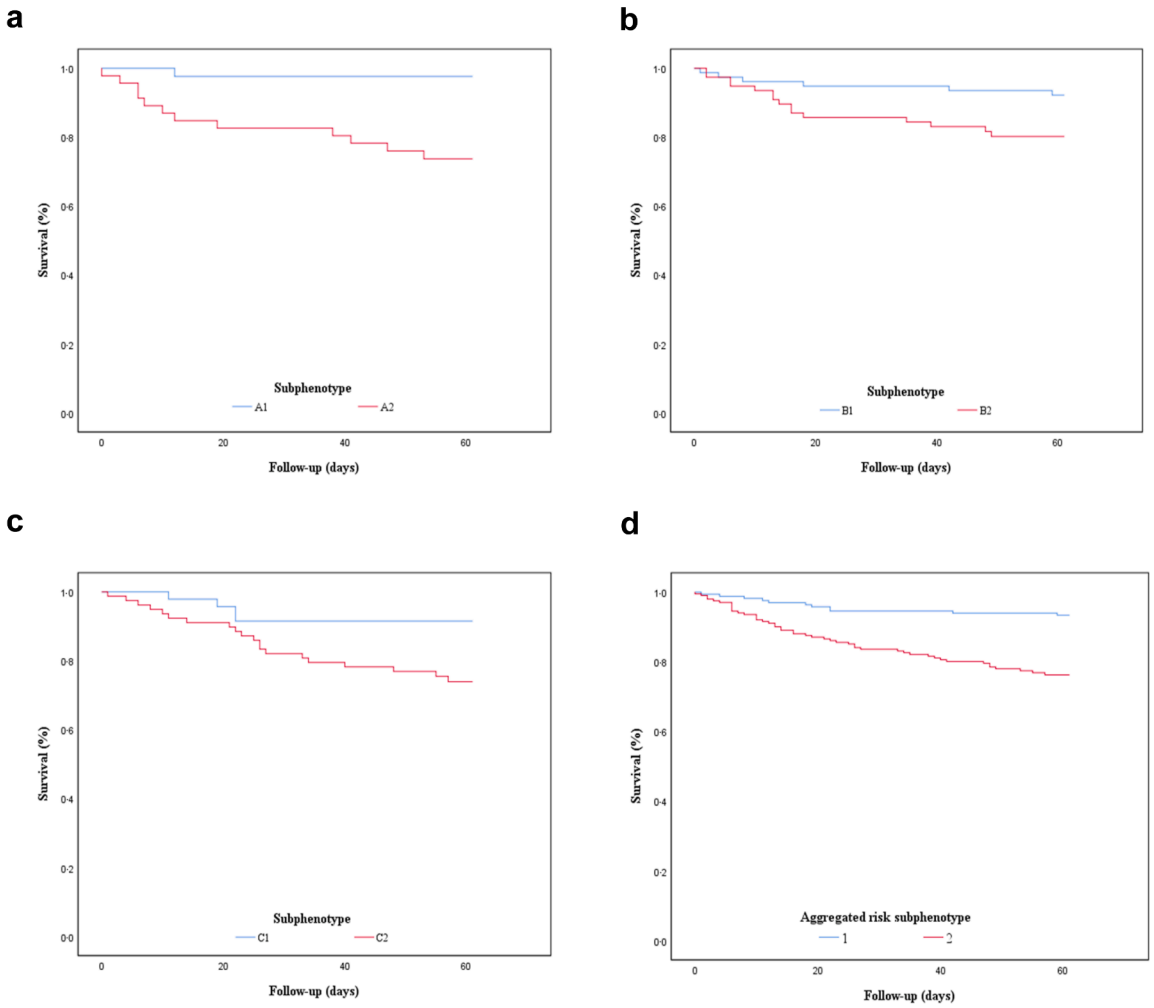

Fig. 1: Kaplan–Meier survival curves over 60 days comparing risk subphenotypes A1 versus A2 (a), B1 versus B2 (b), C1 versus C2 (c), and aggregated risk subphenotypes (d). (a) Log-rank: p = 0·002; (b) log-rank: p = 0·029; (c) log-rank: p = 0·021; (d) log-rank: p < 0·001.

(difference –43·4%, 95% CI –72·9 to –14·0 in favour of adjunctive therapy; p = 0·007) (Table 3, Supplementary Figure S4B). In this subgroup, the estimated NNT to prevent one death at 60 days was 4·5, and the NNT to achieve one additional treatment success at week 8 was 2·3.

Details regarding the most frequent adverse events experienced by patients in each treatment group are provided in Supplementary Table S5.

In the subgroup of patients with low-risk subphenotype and uncomplicated SAB, the DOOR analysis estimated a 54·8% probability (95% CI 45·4%–64·2%) that a randomly selected patient receiving monotherapy would have a better outcome ranking than a patient receiving adjunctive fosfomycin. Conversely, in the subgroup with high-risk subphenotype and complicated bacteraemia, this probability was only 30·8% (95% CI 17·1%–44·4%), indicating that a patient receiving adjunctive fosfomycin is significantly more likely to have a better outcome ranking (Fig. 3 and Supplementary Figure S5).

A sensitivity analysis performed on the per-protocol population yielded results consistent with the primary analysis across the risk strata (Supplementary Table S6). Specifically, the survival benefit signal in the high-risk/complicated subgroup was maintained.

Discussion

This study provides the first external validation of the FEN-AUREUS risk subphenotypes[11] using pooled data from two RCTs in SAB,[20,21] extending the evaluation to long-term outcomes. We confirmed that high-risk subphenotypes (A2, B2, and C2) were consistently associated with higher 60-day and 30-day mortality compared with their low-risk counterparts (A1, B1, and

	Total n/N (%)	All-cause 30-day mortality			All-cause 60-day mortality		
		Deceased n/N (%)	RR versus reference (95% CI)	p	Deceased n/N (%)	RR versus reference (95% CI)	p
Aggregated risk subphenotypes							
Low-risk subphenotype 1	166/369 (45·0)	9/166 (5·4)	Reference	0·02	11/166 (6·6)	Reference	<0·001
High-risk subphenotype 2	203/369 (55·0)	33/203 (16·3)	3·00 (1·48–6·09)		47/203 (23·2)	3·49 (1·87–6·52)	
Complicated bacteraemia (IDSA)							
Uncomplicated	266/369 (72·1)	25/266 (9·4)	Reference	0·05	33/266 (12·4)	Reference	0·005
Complicated	103/369 (27·9)	17/103 (16·5)	1·76 (0·99–3·11)		25/103 (24·3)	1·96 (1·23–3·12)	
Aggregated risk subphenotypes + complicated bacteraemia (IDSA)							
Low-risk subphenotype 1 + uncomplicated	107/369 (29·0)	3/107 (2·8)	Reference	<0·001	3/107 (2·8)	Reference	<0·001
Low-risk subphenotype 1 + complicated	59/369 (16·0)	6/59 (10·2)	3·63 (0·94–14·00)		8/59 (13·6)	4·84 (1·33–17·54)	
High-risk subphenotype 2 + uncomplicated	159/369 (43·1)	22/159 (13·8)	4·94 (1·52–16·08)		30/159 (18·9)	6·73 (2·11–21·49)	
High-risk subphenotype 2 + complicated	44/369 (11·9)	11/44 (25·0)	8·92 (2·61–30·43)		17/44 (38·6)	13·78 (4·25–44·67)	

Table 2: **All-cause 30- and 60-day mortality by aggregated risk subphenotypes and IDSA complicated bacteraemia in the pooled individual-participant dataset.**

C1). These associations remained significant after multivariable adjustment for study centre and the presence of complicated bacteraemia, reinforcing the robustness and external validity of the FEN-AUREUS classification as a prognostic framework in SAB.

Clinical subphenotypes provide a promising approach for stratifying patients with infectious diseases into subgroups with more homogeneous disease trajectories.[23–26] Recent studies have identified distinct subphenotypes in SAB.[11,27] In a study including patients from the ARREST trial, clinical and microbiological outcomes varied among patients receiving rifampicin according to their clinical phenotype.[27] The FEN-AUREUS study developed a simple and pragmatic

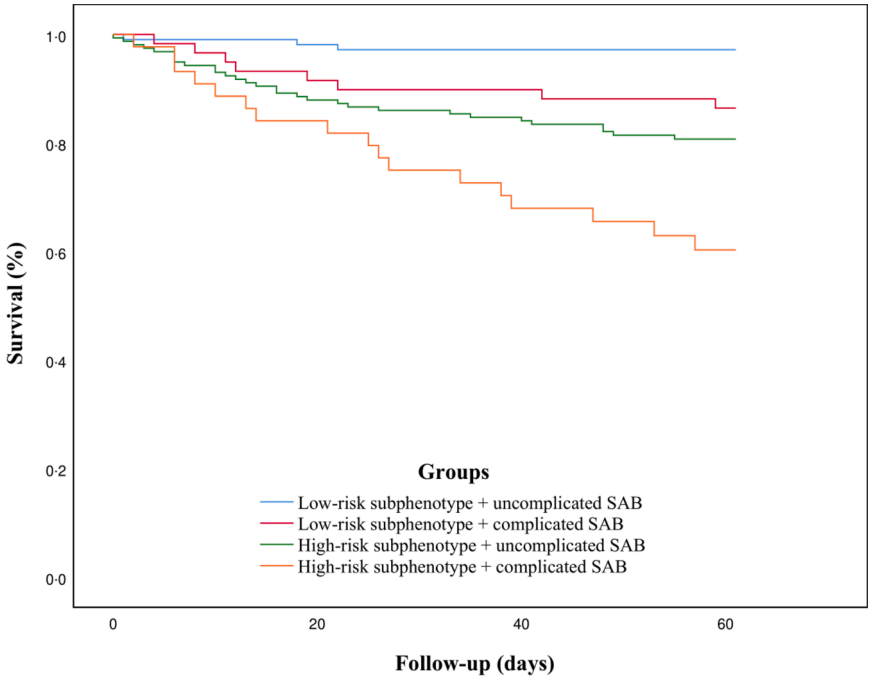

Fig. 2: Kaplan–Meier survival curves by combined risk subphenotype and complicated bacteraemia status (log-rank p < 0·001).

Aggregated subphenotypes	IDSA criteria	Treatment	Total	30–day mortality			60–day mortality			Treatment success at week 8		
				Deceased n/N (%)	Treatment difference (95% CI)	p	Deceased n/N (%)	Treatment difference (95% CI)	p	Success n/N (%)	Treatment difference (95% CI)	p
Low–risk subphenotype (N = 166)	Uncomplicated (N = 107)	Monotherapy	48	1/48 (2·1)	−1·3% (−7·4 to 4·8)	0·68	1/48 (2·1)	−1· 3% (−7·4 to 4·8)	0·68	43/48 (89·6)	−0·2% (−11·8 to 11·3)	0·97
		Adjunctive fosfomycin	59	2/59 (3·4)			2/59 (3·4)			53/59 (89·8)		
	Complicated (N = 59)	Monotherapy	32	4/32 (12·5)	5·1% (−10·0 to 20·2)	0·52	6/32 (18·8)	11·3% (−5·4 to 28·1)	0·20	25/32 (78·1)	−10·8% (−29·4 to 7·8)	0·27
		Adjunctive fosfomycin	27	2/27 (7·4)			2/27 (7·4)			24/27 (88·9)		
High–risk subphenotype (N = 203)	Uncomplicated (N = 159)	Monotherapy	80	8/80 (10·0)	−7·7% (−18·4 to 3·0)	0·16	12/80 (15·0)	−7·8% (−19·9 to 4·3)	0·21	49/80 (61·3)	6·8% (−8·5 to 22·1)	0·38
		Adjunctive fosfomycin	79	14/79 (17·7)			18/79 (22·8)			43/79 (54·4)		
	Complicated (N = 44)	Monotherapy	31	8/31 (25·8)	2·7% (−24·9 to 30·3)	0·85	14/31 (45·2)	22·1% (−6·8 to 50·9)	0·17	8/31 (25·8)	−43·4% (−72·9 to −14·0)	0·007
		Adjunctive fosfomycin	13	3/13 (23·1)			3/13 (23·1)			9/13 (69·2)		
		Total	**369**	**42**			**58**			**254**		

Table 3: **Comparison of 60–day mortality and treatment success by IDSA classification and FEN–AUREUS subphenotypes, stratified by monotherapy versus adjunctive Fosfomycin.**

bedside tool for early risk stratification of patients with SAB into subphenotypes with markedly different mortality, using variables readily available within the first 24 h after bacteraemia onset.[11] This framework has the potential to enhance prognostication and support more personalised therapeutic approaches in SAB.

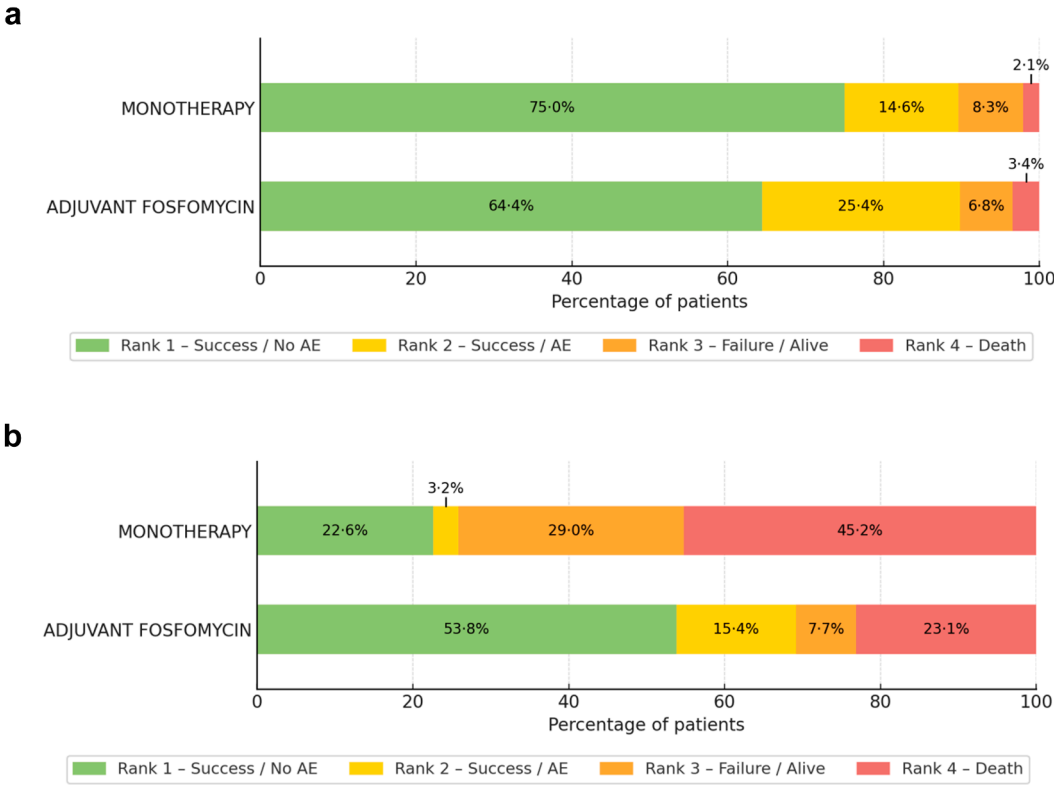

Fig. 3: Distribution of DOOR categories in patients with *Staphylococcus aureus* bacteraemia according to clinical risk groups: (a) low-risk uncomplicated and (b) high-risk complicated. Rankings are ordered from most to least favourable outcome: (Rank 1) Treatment success at week 8 with no adverse events, (Rank 2) Treatment success at week 8 with adverse events, (Rank 3) No treatment success at week 8 and no mortality at day 60, and (Rank 4) Mortality at day 60.

Our findings indicate that although the IDSA "complicated/uncomplicated" classification remains clinically valuable, it does not fully capture the heterogeneity of host risk and disease severity. This limitation may be addressed by complementing it with the early FEN-AUREUS risk subphenotypes. Crucially, this relationship extends beyond antibiotic selection: identifying high-risk patients within the first 24 h should trigger intensified diagnostic work-up and closer clinical monitoring, while the IDSA criteria remain essential in guiding treatment strategy—consistent with contemporary clinical practice guidelines—both at baseline and on reassessment at $\geq$72 h, when complication status becomes ascertainable. By integrating both approaches, we identified four SAB patient groups with progressively increasing mortality and decreasing treatment success: low-risk, uncomplicated; low-risk, complicated; high-risk, uncomplicated; and high-risk, complicated. Notably, patients in the low-risk, uncomplicated group exhibited 60-day mortality below 3% and treatment success exceeding 89%, suggesting monotherapy may suffice for this substantial subgroup, which comprised 29% of the cohort. The DOOR analysis supported this interpretation, indicating a trend toward more favourable outcomes with monotherapy compared to adjunctive fosfomycin.

By contrast, patients with both high-risk subphenotypes and complicated SAB had markedly worse outcomes. In this subgroup, adjunctive fosfomycin was associated with significantly higher treatment success and a lower 60-day mortality compared with monotherapy, although this mortality difference did not reach statistical significance. These findings warrant confirmation in larger cohorts, as the current study may have been underpowered to detect differences in this specific subgroup. Importantly, the DOOR analysis—integrating mortality, treatment success, and adverse events—also supported a potential benefit in this subgroup, primarily driven by the higher rates of treatment success. Regarding the intermediate risk groups, however, results were heterogeneous; therefore, specifically designed trials are required to confirm these observations and establish definitive strategies for these scenarios.

Consequently, regarding clinical implementation, our data provide robust evidence for antimicrobial stewardship in the large subset of patients with low-risk/uncomplicated SAB. In this group, adjunctive fosfomycin offered no benefit but increased adverse events; therefore, findings support a strategy to avoid initiating or de-escalate combination therapy in these patients, prioritizing safety. Conversely, for the high-risk/complicated phenotypes, these results provide a rational basis to consider adjunctive fosfomycin on a case-by-case basis, weighing the potential survival benefit against toxicity, rather than applying a universal approach This study has limitations inherent to its design. First, this is an exploratory, post-hoc pooled analysis of two RCTs with differences in patient populations and protocols. Consequently, the stratification combining FEN-AUREUS subphenotypes with IDSA criteria was not pre-specified, and no formal adjustments for multiplicity were applied. Second, the definition of complicated bacteraemia relies on clinical events occurring after randomisation (e.g., persistent bacteraemia), which could theoretically be influenced by the study treatment, introducing a potential for selection bias. However, since effective treatment would likely reduce the progression to 'complicated' status, the remaining patients in the intervention arm would represent the most severe cases. Thus, the superior outcomes observed with adjunctive fosfomycin in this subgroup likely represent a conservative estimate of its efficacy. Third, the DOOR endpoint was constructed post-hoc using available clinical outcomes. Nevertheless, we devised an ordinal hierarchy designed to reasonably balance efficacy (survival and cure) against toxicity, capturing the primary trade-off evaluated in this study. Conversely, a strength of this study is that it highlights how RCTs often enrol heterogeneous patient populations predominantly composed of low-risk individuals. This heterogeneity may partly explain why published trials have often failed to demonstrate differences between combination therapy and monotherapy.[12–18] Moreover, our findings identify a well-defined high-risk subgroup with significantly greater mortality, emphasising the critical need to optimise management and prioritise the most effective treatment strategies for these patients.

In summary, this study provides the first external validation of the FEN-AUREUS risk subphenotypes in RCT cohorts of SAB, confirming their prognostic value for mortality. Combining early clinical subphenotypes with established IDSA criteria for complicated infection enables precise stratification of patients into risk groups with distinct outcomes and therapeutic responses. Importantly, our exploratory analysis suggests that adjunctive fosfomycin may improve outcomes in the high-risk, complicated subgroup, while low-risk uncomplicated patients achieved favourable outcomes with monotherapy. Taken together, these findings could represent a paradigm shift in the management of SAB—from a one-size-all approach to a more individualised strategy—highlighting the potential of this dual classification framework to optimise patient care and inform the design and interpretation of future clinical trials.

Contributors

Study conception and design: FEV, BGG and JC. Acquisition of data: all members of the BACSAFO/FEN-AUREUS group. Analyses and interpretation of data: FEV, BGG and JC. Manuscript draft: FEV, BGG and JC. Manuscript critical revision: all members of the BACSAFO/FEN-AUREUS group. Obtaining funds: JC, MP, JR-B. FEV, BGG and JC verified all data and were responsible for the decision to submit the manuscript.

Data sharing statement

Raw anonymised data relating to primary and secondary outcomes and safety may be shared upon request with researchers who provide a methodologically reasonable proposal. Requests for data should be sent to the corresponding author (JC). Interested researchers must obtain the approval of the Bellvitge University Hospital Ethics Committee.

Declaration of interests

FEV and JC received honoraria for educational purposes by MSD. MP received a research grant from Laboratorios ERN. JL-C received grants from Astra Zeneca, GSK and Pfizer, and honoraria for educational purposes from Astra Zeneca, Pfizer, MSD, Menarini, and Advanz. SG-Z has received a grant from the Instituto de Salud Carlos III (PI21/000509). LEL-C has been a scientific advisor for Angelini and a speaker for Angelini, ViiV, Gilead and Correvio. OG has received a grant from Pfizer (grant number 60043821). JG-L, GE, AV, EA-M, RE-S, MTP-R, DR-P, AJ-S, GG-P, JR-B, and BG-G have nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101611.

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