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Study on the utility of a statewide counselling programme for improving mortality outcomes of patients with *Staphylococcus aureus* bacteraemia in Thuringia (SUPPORT): a study protocol of a cluster-randomised crossover trial

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ABSTRACT

Introduction: *Staphylococcus aureus* bacteraemia (SAB) is a frequent infection with high mortality rates. It requires specific diagnostic and therapeutic management such as prolonged intravenous administration of antibiotics and aggressive search for and control of infectious sources. Underestimation of disease severity frequently results in delayed or inappropriate management of patients with SAB leading to increased mortality rates. According to observational studies, patient counselling by infectious disease consultants (IDC) improves survival and reduces the length of hospital stay as well as complication rates. In many countries, IDC are available only in some tertiary hospitals. In this trial, we aim to demonstrate that the outcome of patients with SAB in small and medium size hospitals that do not employ IDC can be improved by unsolicited ID phone counselling. The SUPPORT trial will be the first cluster-randomised controlled multicentre trial addressing this question.

Methods and analysis: SUPPORT is a single-blinded, multicentre interventional, cluster-randomised, controlled crossover trial with a minimum of 15 centres that will include 250 patients with SAB who will receive unsolicited IDC counselling and 250 who will receive standard of care. Reporting of SAB will be conducted by an electronic real-time blood culture registry established for the German Federal state of Thuringia (ALERTSNet) or directly by participating centres in order to minimise time delay before counselling. Mortality, disease course and complications will be monitored for 90 days with 30-day all-cause mortality rates as the primary outcome. Generalised linear mixed modelling will be used to detect the difference between the intervention sequences. We expect improved outcome of patients with SAB after IDC.

Ethics and dissemination: We obtained ethics approval from the Ethics committee of the Jena University Hospital and from the Ethics committee of the State Chamber of Physicians of Thuringia. Results will be published in a peer-reviewed journal and additionally disseminated through public media.

Trial registration number: DRKS00010135.

Strengths and limitations of this study

- First randomised controlled trial investigating the impact of infectious disease counselling for patients with *Staphylococcus aureus* bacteraemia.
- Inclusion of smaller and rural hospitals. The majority of the studies on the impact of infectious disease counselling have been conducted at tertiary care centres until now.
- Provision of infectious disease counselling for hospitals without access to infectious disease specialists in rural areas versus standard of care.
- Possibly up to 4–5 days' time delay between blood cultures taken and intervention.
- Telephone consultation only, no bedside infectious disease counselling.

INTRODUCTION

Bloodstream infections (BSI) caused by *Staphylococcus aureus* (SAB) are common infections associated with high mortality rates.[1] *Staphylococcus aureus* is one of the leading causes of healthcare-associated and community-acquired BSI worldwide. SAB causes significant morbidity, mortality and healthcare costs and with regard to complications, diagnosis and treatment, SAB substantially differs from BSI caused by other pathogens.[1]

Appropriate treatment of patients with SAB requires at least 2 weeks of appropriate intravenous therapy, source control and detailed evaluation for metastatic infection or endocarditis.[2 3] Evidence derived from retrospective studies and case series suggests that involvement of an infectious diseases (ID) specialist (ID consultant/consultation, IDC) in patients' care improves the outcome of the patients and reduces overall antibiotic usage, complications and length of hospital stay.[2 3]

These results are supported by a recent meta-analysis by Vogel *et al*,[2] providing further evidence that IDC improves adherence to current treatment guidelines, such as treatment with long-term intravenous antibiotics and evaluation of infective endocarditis, as well as reduces the 30-day mortality rates from 26% to 12% (RR 0.53, 95% CI 0.43 to 0.65).

However, available evidence is exclusively derived from retrospective non-randomised studies and therefore bears a high inherent risk of bias.[4–10] To the best of our knowledge, prospective controlled randomised trials comparing the effects of ID consultation versus standard of care treatment in patients with SAB have not been performed. In addition, the majority of patients are hospitalised in small and medium-sized community and rural hospitals, which do not have access to bedside IDC due to shortage of ID specialists. Hence, unsolicited telephone consultation by an ID specialist may be an option to substantially improve patient care in the current setting. One retrospective study compared bedside versus ID phone consultations versus no IDC for patients with *S. aureus* bacteraemia.[11] Telephone consultation was inferior to bedside consultation. However, given the risk for bias of the study (retrospective, unmatched cases, different group size) and the limited number of patients in the groups with telephone consultation and no IDC, no firm conclusion can be drawn.

With the SUPPORT trial, we aim at investigating whether an ID specialist telephone counselling programme improves the survival of patients with SAB in the Federal State of Thuringia by pointing to a bundle of evidence-based quality-of-care indicators for the management of SAB.[3] This will be the first cluster-randomised controlled multicentre trial with a crossover design investigating the impact of IDC for patients with SAB.

Box 1 Quality-of-care indicators for patients with *Staphylococcus aureus* bacteraemia

- Follow-up blood cultures within 2–4 days after initiation of appropriate antibiotic therapy
- Early source control (such as removal of infected intravascular catheters and abscess drainage) within 72 hours
- Transoesophageal echocardiography in patients with clinical indications applying the VIRSTA score[18]
- Early (within 7 days after diagnosis) use of intravenous narrow spectrum β-lactam antibiotics for methicillin-susceptible *Staphylococcus aureus* and antibiotic combination therapy using rifampicin, fosfomycin and concomitant oral combination therapy, for example, rifampicin+cotrimoxazole in patients with implants, for example, intracardiac devices, prosthetic valves or joints
- Adjustment of vancomycin dose according to trough levels in methicillin-resistant *S. aureus* infections (15–20 mg/L)[19]
- Treatment duration according to the complexity of infection, for example (2 weeks for uncomplicated and 4–6 weeks for complicated SAB)

METHODS AND ANALYSIS

Study design

SUPPORT is a single-blinded, multicentre interventional, cluster-randomised, controlled crossover trial that includes hospitals in the federal state of Thuringia, Germany (population: 2.249 million). Participating hospitals (minimum 15 centres) will be randomised to two sequences A-B or B-A. A is the intervention (described below) and B is the control. During the IDC intervention, attending physicians of patients with SAB will receive unsolicited ID telephone consultation from an external ID specialist, evaluating the disease history, symptoms and risk factors of the patient pointing to a bundle of evidence-based quality-of-care-indicators (QCIs) for the management of SAB (box 1).[3] All cases are discussed among the ID team during daily meetings at the Jena University Hospital (JUH) in order to obtain consent and reduce heterogeneity in treatment recommendations. Written recommendations will then be faxed to the treating physician. Hospitals that are in the control phase will not receive phone consultations or recommendations (figure 1). Patients with SAB will only be included into the trial after signing written informed consent. Patients who cannot sign informed consent due to severe infection or pre-existing medical conditions can participate in the trial if consent by proxy by a court-appointed legal guardian is provided.

After the first study phase, for example, after 15 included patients or latest 12 months after trial initiation at the study centre, hospitals in the previous control group will receive the same support as the intervention group, whereas the hospitals in the previous intervention group will no longer receive unsolicited ID telephone consultations. However, adherence to the selected QCIs will be monitored to assess the sustained effect of the consultations. The protocol of the trial was planned following the SPIRIT statement.[12] The trial data will be reported in accordance with the CONSORT statement.[13]

Study population and outcome measures

Considered for trial inclusion are patients ≥18 years of age with *S. aureus* bacteraemia reported via the statewide Thuringian ALERTSNet blood culture database.[14 15] Patients will be identified by daily review of microbiological blood culture reports provided by ALERTSNet.[15] In order to minimise time delay before counselling,

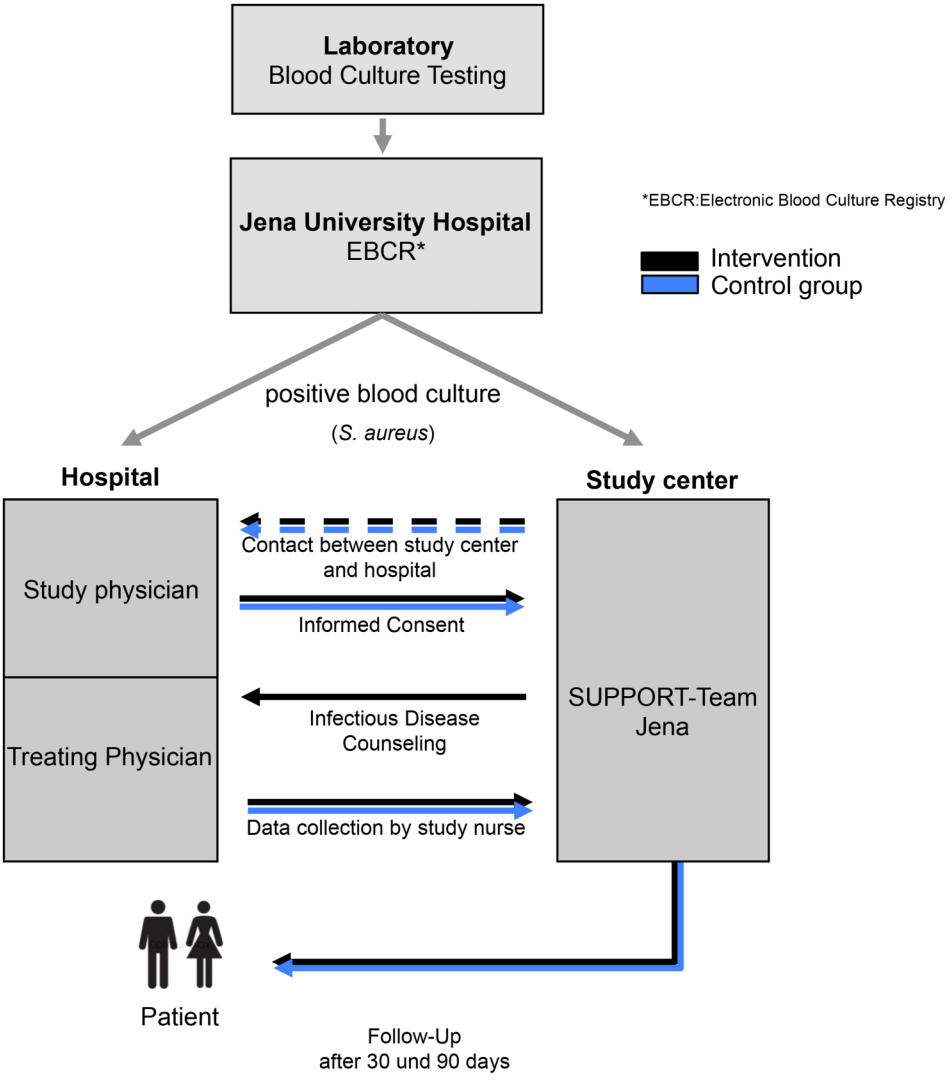

Figure 1 Study design of the SUPPORT trial.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	■ Age ≥ 18 years ■ At least one positive blood culture with isolation of *Staphylococcus aureus* ■ Written informed consent
Exclusion criteria	■ Blood cultures positive for other bacteria than *S. aureus* ■ In polymicrobial infections, one of the isolates must be *S. aureus* ■ *Staphylococcus aureus* infections without bacteraemia ■ Patients who receive palliative care and therapy limitations or with a life expectancy of <90 days due to another underlying disease

direct contact by trained physicians from the participating centres is also possible as ALERTSNet reporting might be associated with a certain time delay. Only one episode per patient will be included. Further episodes of SAB in one patient will only be included into the study if they occur >3 months after the previous SAB episode and if there is no evidence of recurrence from a deep-seated infection of the previous episode.

Patients with a life expectancy of <90 days or patients who receive palliative care (treatment limitations due to underlying medical conditions or end-stage cancer) will be excluded from the study (table 1). The primary outcome is the 30-day all-cause mortality. Secondary outcome measures are (1) adherence to six selected QCI indicators measured as the proportion of cases in which the recommended action was performed; (2) 90-day all-cause mortality; (3) 90-day recurrence rate; (4) progression to sepsis and septic shock within 7 days[16] and (5) development of secondary septic foci within the follow-up period.

Proposed sample size

Since the unit of randomisation is the centre, sample size and statistical power considerations for a cluster-randomised crossover trial largely depend on the variation in outcomes between centres. If this variation is large, then more centres are needed, and the number

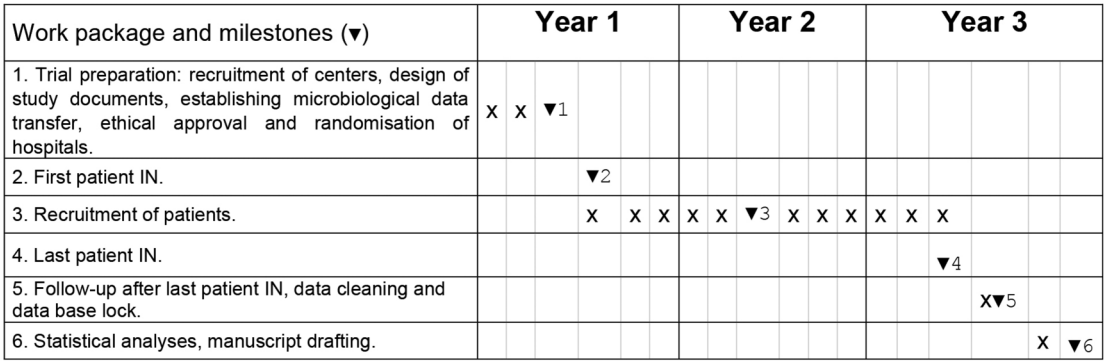

Figure 2 Timeline of the SUPPORT trial. Milestones are defined as ▼1 trial preparation (month 6); ▼2 inclusion of the first patient (month 7); ▼3 inclusion of the 250th patient (month18); ▼4 inclusion of the last patient (month 30); ▼5 end of follow-up and closure of database (month 32); ▼6 submission of the scientific manuscript (month 36).

of patients per centre/cluster is less relevant. The sample size for the present cluster-randomised crossover design was calculated for the binary primary outcome (30-day all-cause mortality) using simulations as described in Reich *et al*.[17] On the basis of a recently published meta-analysis,[2] we estimated that the risk ratio between the two groups will most likely range between 0.5 and 0.7. If this trial includes 15 centres with an average number 2×15 patients each, that is, 15 patients in 1 period, the study will be well powered (>80%) to detect true risk ratios of 0.5 for a control group 30-day all-cause mortality rate of 0.25–0.35 and moderate to small between centre variation. We expect that the rate of patients with loss to follow-up will be negligible, as follow-up visits will only be conducted by telephone calls, which can also be answered by relatives or primary care physicians.

Study sample and recruitment

For SAB, incidences are reported with 15–40 cases per 100 000 population.[2] This is in accordance with SAB incidences from the 1375-bed JUH, Thuringia, Germany, with 220 patients with SAB treated in 2015. Data from smaller cooperating Thuringian hospitals reveal comparable incidence rates (SW, personal communication). A minimum of 15 hospitals participating in ALERTSNet[15] will be recruited for this trial allowing to achieve an overall sample size of 500 patients (30 patients per hospital) during a 2-year recruitment period (see the Proposed sample size section). Recruitment of the trials started in July 2016. A trained study physician at each participating hospital will collect informed consent. The timeline is given in figure 2.

Randomisation, follow-up and data protection

Participating hospitals will be randomised to two sequences A-B or B-A, where A is the intervention and B is the control. Prior to the trial initiation, an independent staff member at the Center for Clinical Studies (JUH) generated a randomisation list for all participating hospitals which was subsequently locked at the Center for Clinical Studies. Patients will be assigned depending on the randomisation result of the hospital and the current status of included patients at the centre. The ID specialist at the JUH will assure implementation of the study assignments. Patients who are transferred to other hospitals during or after inclusion into the trial will be analysed according to the intention-to-treat principle. Patients who are transferred to other hospitals during or after inclusion into the trial will be analysed in an intention-to-treat analysis. Patients with SAB who have been transferred before being included into the trial, for example, from a hospital in the intervention phase to a hospital in the observation phase, will not be included. Only the patients will be blinded to the allocation. Patients will be blinded during the entire study period, that is, 90 days. Unblinding will be only performed on request thereafter. A trained study nurse will collect patient-related clinical data at the centres after the discharge of the patients. Patients will be followed up by phone calls 30 and 90 days after the first *S. aureus*-positive blood culture. In case the patient cannot be reached, informed consent is also provided to contact the primary care physician or a person available under the same telephone number. A questionnaire is provided in box 2. All study-related information will be kept in two different places at the JUH with controlled and limited access. Screening lists and a patient

Box 2 Questionnaire for 30-day and 90-day follow-up

- Could contact with the patient/relative/primary care physician be established?
- Has the patient died?
- If yes, when and what was the cause of death?
- Is the patient currently admitted to a hospital?
- Has the patient been admitted to the hospital since discharge/30-day follow-up?
- If yes, when, and what was the reason for admission.
- Are there any new symptoms since discharge/30-day follow-up?
- If yes, what are the new complaints or symptoms?

identification file will be kept at the office of the Center for Infectious Disease and Hospital Hygiene (JUH). Case report forms are kept in a locked drawer in the room of the study nurses that is located in a separate building. Access to local electronic databases is password restricted. Passwords are only provided to individuals directly working with the trial data.

Data analysis

Data will be analysed after inclusion of the last patient, data cleaning and the official database lock will be performed by a statistician who was not involved in the recruitment of patients, counselling of the treating physicians or data collection. We will use generalised linear mixed modelling to detect the difference in 30-day all-cause mortality rates between the intervention or control treatment phases. This model is suited to address the clustering effects by centre and the crossover design. Treatment (intervention vs control) and period (two levels) will be modelled as fixed effects, and centres (clusters) will be modelled as random effects while individual-level variability in covariates is ignored. The statistical hypotheses (null H_0 and alternative H_1) for the primary outcome are H_0: $\beta=0$ against H_1: $\beta\neq0$, where β is the fixed 30-day all-cause mortality rate effect between the two treatment conditions. H_0 can be rejected if the two-sided p value related to the Wald test statistic for the treatment effect is smaller than $\alpha=0.05$ (two-sided). No multiple testing issues arise for the confirmatory analysis, which will be performed in the intention-to-treat analysis set. We will perform explorative sensitivity analysis of the primary outcome which includes models that additionally adjust for individual-level covariates (sex, age, acute severity of illness (linear) and Charlson comorbidity index (linear)), per-protocol analyses and subgroup analyses stratified by centre, sex, worst/best-case scenario analyses in the case of missing data of the primary efficacy end point, and analyses for potential carryover effects. All analyses of the secondary outcomes will also be explorative and follow the modelling approach of the primary outcome; expected modifications are required for non-binary outcomes.

Clinical data collection

No data beyond clinical routine documentation have to be assessed. A specialised study nurse from the JUH will collect and enter the data into a case report form at the participating centres and transfer the data into an electronic case report form at the JUH. It is intended to collect the data within 30 days after inclusion of the patient. Harms that could occur with the advised medication or intervention are documented in the case report form. All drugs or interventions that will be advised during IDC are routinely used in hospitals and have known risks. Follow-up phone calls scheduled 30 and 90 days after the diagnosis of SAB will also be performed by the study nurse.

DISSEMINATION

The German Infection Protection Act calls for ID specialists to counsel primary care physicians in the treatment of infectious diseases to improve management and tackle the threat of antibiotic resistance. Since there is a lack of ID specialists, support may serve as a model for other rural areas in Germany. Results of the SUPPORT trial will be published in a peer-reviewed journal and additionally disseminated through public media.

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Competing interests SW received speakers' fees from MSD. SH received speakers' fees from Pfizer, MSD and Astra Zeneca. MWP has participated in international advisory boards of Pfizer, Novartis, Basilea and Cubist and received speakers' fees from them. FMB has participated in international advisory boards of MSD and received speakers' fees from MSD, Pfizer and ThermoFisher Scientific. CF received speakers' fees from Pfizer, MSD, Basilea and Gilead.

Ethics approval Ethics committee of the University Hospital Jena (No. 4608-11/15), and by Ethics committee of the State Chamber of Physicians of Thuringia (Jena-Maua, Germany; No. 53394/2016/72).

Provenance and peer review Not commissioned; externally peer reviewed.

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