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Implementation of a Bundle for Gram-Negative Bloodstream Infection: Impact on 30-Day Mortality Analyzed with a Path Model

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INTRODUCTION

Gram-negative bacteria are the first cause of community bacteremia and the second cause of nosocomial bacteremia with increasing incidence, relevant morbidity and mortality. The current lack of international guidelines and/or evidence-based care bundles focused on Gram-negative bloodstream infection (GN-BSI) led to challenging management.

OBJECTIVES

Our aim was to verify whether implementing a bundle in the management of GN-BSI which comprised follow-up blood culture (FUBC), diagnosis imaging (DI) and source control (SC), optimized antibiotic administration (OAA) and shortened treatment duration for uncomplicated BSIs reduced mortality after a GN-BSI event.

METHODS

The study population included patients with monomicrobial GN-BSI aged ≥18 years enrolled at IRCCS Azienda Ospedaliero-Universitaria di Bologna. From January 2017 to December 2019 patients were administered standard clinical practice (pre-phase); from January 2022 to December 2023 (post-phase) all patients with monomicrobial GN-BSI were managed according to the predefined bundle designed to provide a structured, standardized approach to GN-BSI management, aimed to reduce mortality and improve patient outcomes. To verify the objective of the study a path model was developed, in which the indicator of the study phase was the exposure of interest, 30-day all-cause mortality was the dependent variable and the indicators of FUBC, DI, OAA and SC were set as mediators. FUBC, DI and OAA were posited as first-level mediators and SC as a subsequent mediator, because the decision to undertake FUBC, DI and OAA stems from the patients' diagnosis, while SC can be undertaken according to FUBC and DI results. Treatment duration was not included in the model because it could be either cause or effect of mortality. The phase indicator was hypothesized as influencing all mediators and the outcome. Several clinical characteristics along with age and gender were included as exogenous variables. From an initial theoretical model, a final model was obtained by discarding non-significant paths and adding paths suggested by modification indices and deemed clinically relevant. Finally, a comparison with other modelling techniques was carried out to verify whether the path model actually added critical information and fitted best to the data.

RESULTS

Overall 3,355 patients were included, 2,092 were managed in the pre-phase and 1,263 with the bundle. Median age was similar (70.4 ± 16.4 vs. 71.2 ± 16.2 years), as the proportion of male patients (55.4% vs. 58.3%). No significant differences were observed in SOFA score, immunosuppression, septic shock incidence, rates of uncomplicated BSI, while the Charlson Comorbidity Index (CCI) was slightly lower in the post-phase (5.57 ± 2.74 vs. 5.79 ± 3.04; p = 0.011). In post-phase patients the BSI acquisition site showed fewer nosocomial or healthcare-associated cases (64.9% vs. 68.3%, p=0.045) and more community-acquired infections. Escherichia coli was the most common pathogen and was less frequent among post-phase patients (47.8% vs. 53.3%; p = 0.002). Among these patients, higher proportions of appropriate empirical therapy (77.0% vs. 69.2%; p <0.001), execution of FUBC within 7 days (55.8% vs. 30.2%; p <0.001), use of DI (90.8% vs. 77.5%; p <0.001) as well as SC (26.3%

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vs. 23.6%, p=0.083) were found, while OAA was administered in similar proportions. Mortality rate at 30 days was slightly higher in patients of the pre-phase (14.1% vs. 12.4%) but non-significant at χ^2 test (p =0.150). The final path analysis model was performed on 3322 patients and used 12 independent and 4 dependent variables. It obtained a very satisfactory fit to the data (RMSEA=0.015, CFI=0.973, TLI=0.953) and explained 32.7% variance of the 30-day mortality variable. The model confirmed that bundle administration was not directly associated with 30-day mortality, however an indirect negative association was found, through imaging: patients of the post-phase were more likely to have DI performed, which in turn was associated to a lower risk of 30-day mortality. The total indirect effect on mortality of being in the post-phase, expressed by standardized coefficient, was -0.050 (p<0.001). DI was positively correlated with FUBC (r=0.285). Other variables significantly affecting mortality (std. effects) were SOFA score (0.275, p<0.001), age (0.234, p<0.001), UTI (-0.172, p<0.001), CCI (0.167, p<0.001), stay in surgery ward at the time of infection (-0.130, p<0.001), BSI nosocomial infection (0.034, p<0.001), carbapenem resistance (0.063, p=0.009) and Pseudomonas spp pathogen (0.045, p<0.001). The relationship between study phase and mortality was not found by a multiple logistic regression model including the same variables used in the path model (std. coefficient 0.004, p=0.882); a treatment-effect lasso logistic model run with 75 variables on 2791 patients of this population obtained an ATE of -0.004 (p=0.798) with a PO mean of 0.137 (p<0.001).

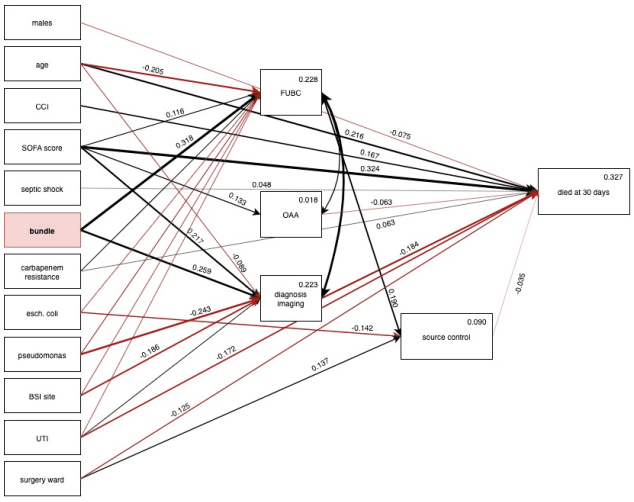

Figure 1. Path model diagram. Arrow lines indicate direct relationships between variables; black arrows represent positive relationships, red arrows represent negative relationships; thickness is proportional to the strength of the relationship, which is written near most of the arrows. Lines with bidirectional arrows indicate correlations between dependent variables. The number inside the box of the dependent variables indicates the R^2.

CONCLUSIONS

Interventions like the bundle described in this study are not inherently affecting mortality directly, because they act by deploying several components that may take place with a predetermined priority and sequence, actually one affecting the other. Rather, they are expected to affect the outcome indirectly by triggering activities that can actually be related to the outcome. We have demonstrated that the bundle activation did decrease the mortality rate of patients with monomicrobial GN-BSI by increasing the use of imaging and of its correlated follow-up blood culture, which in turn were related to lower mortality. Indirect effects cannot be estimated by traditional modelling techniques like multiple regression, therefore we advocate the use of path modeling in clinical settings involving temporally related activities.

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