Management of patients with bloodstream infections (BSI) is challenging. Early administration of active empirical therapy (which must be compatible with avoidance of excessive use of broad spectrum antibiotics) with adequate dosing of antibiotics, support therapy if needed, active search for the source and early source control, close follow-up of complications, de-escalation and switch to oral therapy whenever possible, and appropriate duration of treatment are key aspects of management. Epidemiological and observational studies have identified the rate of pathogens and resistance in different patient populations, and predictors for bad outcomes. However, morbidity and mortality among patients with BSI due to multidrug-resistant (MDR) and extensively drug resistant (XDR) gram negative bacteria (GNB) is unacceptably high. This is probably be due to the lower probability of receiving active empirical therapy and the limited possibilities for definitive therapy, leading to a new paradigm in which individualised therapy is key. Because BSI due to MDR and XDR GNB occur in patient admitted to most hospital services, bacteraemia programs, in which unsolicited advice and follow-up is provided by teams including infectious diseases specialists and clinical microbiologists, are being increasingly implemented in hospitals. A close collaboration between infectious diseases specialists and clinical microbiologists is key in order to provide early relevant information regarding identification and susceptibility of the pathogens and define the best treatment options in each case. Identification of key, evidence-based indicators may facilitate the structured applicability of such interventions to different hospitals. Real-time data sharing among hospitals may provide important, updated information about the best options of therapy for difficult-to-treat cases.