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ARTICLE

Suitability of initial antibiotic therapy for the treatment of bloodstream infections and the potential role of antibiotic management teams in improving it

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Abstract Hospital antibiotic management teams (AMTs) have been recommended, but, in France, their concrete implementation remains scarce and their effectiveness largely unevaluated. The objective of this investigation was to evaluate the appropriateness of antibiotic therapy (AT) for bloodstream infections (BSIs) at a 950-bed university teaching hospital, and assess the role of an AMT in improving it. A prospective analysis of all significant BSIs occurring outside of the intensive care unit (ICU) during an 18-month period was carried out. AT was deemed effective if at least one prescribed antibiotic was effective in vitro, and appropriate if it was consistent with local recommendations. Out of 574 BSIs, 512 were evaluated: 231 community-acquired, 206 nosocomial, and 75 healthcare-associated. For 219 (42.8%) BSIs, the AT initiated prior to AMT intervention proved to be effective and appropriate, inappropriate but effective in 136 (26.5%), and ineffective or absent in 157 (30.7%). In the multivariate analysis, hospital-acquired and other healthcare-associated BSIs, as well as catheter-borne (CB) infections, were associated with inappropriate or absent AT. A recommendation from the AMT was given and followed in 233 (94%) out of 249 BSIs requiring intervention. Initially, two-thirds of BSIs outside the ICU did not receive appropriate AT. Healthcare-associated BSIs should, therefore, be the priority target of AMTs.

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Introduction

Of all infections, bloodstream infections (BSIs) have the highest impact on mortality, morbidity, and healthcare costs [1]. Empirical antibiotic therapy is the rule for treating severe sepsis, as early treatment has been shown to reduce infection-related mortality [2–4]. Ideally, appropriate antibiotic therapy must take into consideration the type and source of the BSI (community-acquired or healthcare-associated), as well as the spectrum and local epidemiology of bacterial resistance.

Several studies have established that empirical antimicrobial therapy was inappropriate in about half of the cases [5]. Although time-consuming, academic detailing is one of the most effective measures in improving antimicrobial therapy. Antibiotic management teams (AMTs) (also referred to in the literature as antibiotic stewardship teams) are used in many hospitals [5–9] . Although they remain scarce within the healthcare system in France, AMTs are

increasingly solicited in order to insure the delivery of an efficient and cost-effective antibiotic therapy. Therefore, in this study, we set out to assess the circumstances in which AMT intervention would be the most suitable and effective in treating BSIs at a large Paris University teaching hospital.

Methods

Bichat–Claude Bernard is a 950-bed adult university teaching hospital that includes all specialties except hematology and neurosurgery, with approximately 35,000 full admissions a year. Since 2007, our AMT has been systematically evaluating the management of BSIs in all of the hospital's clinical units, outside of the medical and surgical intensive care units (ICUs). The AMT was put in place in 2007, and operates weekdays from 9 am to 7 pm, in response to solicitation by hospital clinicians, microbiologists, and pharmacists. It is composed of two infectious diseases physicians (devoting roughly two-thirds of their time to these duties), a pharmacist, as well as representatives from the bacteriology and the infection control units.

This study spans an 18-month period extending from January 2008 to June 2009, and included those patients presenting all epidemiologically [10] and clinically significant blood culture (BC) results. A bacteremia was defined as epidemiologically significant if one or more BC was positive with a known pathogen, and at least two BCs were positive with the same microorganism taken from blood samples obtained within a 48-h period for the following microorganisms: coagulase-negative staphylococci, *Corynebacterium* sp., *Micrococcus* sp., *Bacillus* sp., *Propionibacterium* sp., or other similar non-pathogenic microorganisms. Also excluded were those patients who could not be followed due to early discharge or death, as well as those presenting non-clinically significant bacteremias, i.e., those epidemiologically significant BCs for which the AMT member and the physician in charge of the patient agreed that antibiotic therapy was simply not warranted.

Because our hospital does not include a Hematology Department, less than ten episodes of fungemia are encountered every year. In addition, these positive BCs are processed in the Mycology Laboratory and are not rapidly available for AMT intervention. Patients with fungal infections were, therefore, excluded from our study.

As part of the standard hospital operating procedures, when a BC is shown to be positive (BacT/Alert, BD Microbiology Systems), the microbiologist immediately alerts the physician in charge of the patient. This notification system operates 7 days a week, from 9 am to midnight; positive BCs obtained after midnight are communicated the next morning. The microbiologist specifies the smear aspect (Gram staining) and, if solicited by the ward physicians, recommends an appropriate course of antibiotic therapy. A physician member of the AMT systematically visited the patient the same day that positive BC results were obtained, except those positive BCs that were clearly contaminated; patients with positive BCs positive during the weekend were visited the following Monday.

The following parameters were collected for this study: hospital unit, patient age and gender, date of collection and transmittal of the first positive BC results, starting date of antibiotic therapy, date of AMT intervention, and, in those cases where the initial course of antibiotic therapy had to be corrected, starting date of appropriate antibiotic therapy. In addition, also noted were the degree and severity of the underlying disease [11], the type of bacteremia (either community-acquired or healthcare-associated) [12], the type of bacterial agent involved, the prevalence of antimicrobial resistance (according to pre-established criteria [http://www.sfm-microbiologie.org/]), as well as the source of the bacteremia. Antibiotic therapy was classified as appropriate if it was administered in accordance with local prescription guidelines, which, themselves, are based on national and international recommendations. It was classified as effective if the antimicrobial treatment included at least one drug that has been shown to be effective in vitro against the bacterium associated with the BSI. An effective course of antibiotic therapy was judged to be "inappropriate" when it fails to conform to local prescription guidelines, and the flexibility margin in this regard was intentionally made narrow. Examples are the use of excessively large spectrum antibiotics (e.g., use of imipenem in treating community-acquired urinary tract infection), errors in the way in which a given antibiotic was administered (e.g., orally administering oxacillin to treat a *Staphylococcus aureus* bacteremia), or dosage errors involving too low antibiotic concentrations.

Continuous variables were presented as mean (± standard deviation [SD]) and categorical variables as percentages. Variables associated with an appropriate antibiotic therapy (as opposed to absent or inappropriate therapy) were compared using univariate and logistic regression multivariate analyses. All tests were bilateral, with p-values <0.05 being considered as significant.

Results

During the study period, 2,051 positive BCs were obtained, corresponding to 1,297 episodes. Of these, 842 were epidemiologically significant BSIs: 268 in patients in the medical or surgical ICU and 574 were in patients outside

these two ICUs (Fig. 1). Of the latter group, 64 cases were excluded (22 represented non-clinically significant episodes and 40 were significant episodes but were not included because of delayed AMT notification). As a result, our study encompassed 512 cases of clinically significant BSIs (231 community-acquired, 206 hospital-acquired, and 75 healthcare-associated). At the time of AMT intervention, antibiotic therapy was found to be appropriate in 219 (42.8%) cases, inappropriate but effective in 136 (26.6%), inappropriate and ineffective in 33 (6.4%), or absent 124 (24.2%) (Table 1).

Of the latter 157 cases (inappropriate and ineffective, in addition to absent therapy), 147 were intervened by the AMT, and their recommendations were ignored in 6 (4.1%) of these cases. Of the 136 cases in which antibiotic therapy was inappropriate but effective, 102 saw AMT intervention, and their recommendations were ignored in 5 (4.9%) of these cases. Overall, AMT recommendations were followed in 233 (94%) out of these 249 interventions.

All appropriate antibiotic therapies were subsequently classified as effective, except in one case: an infection whose treatment followed guidelines, but failed due to resistance conferred by an associated extended-spectrum beta-lactamase (ESBL).

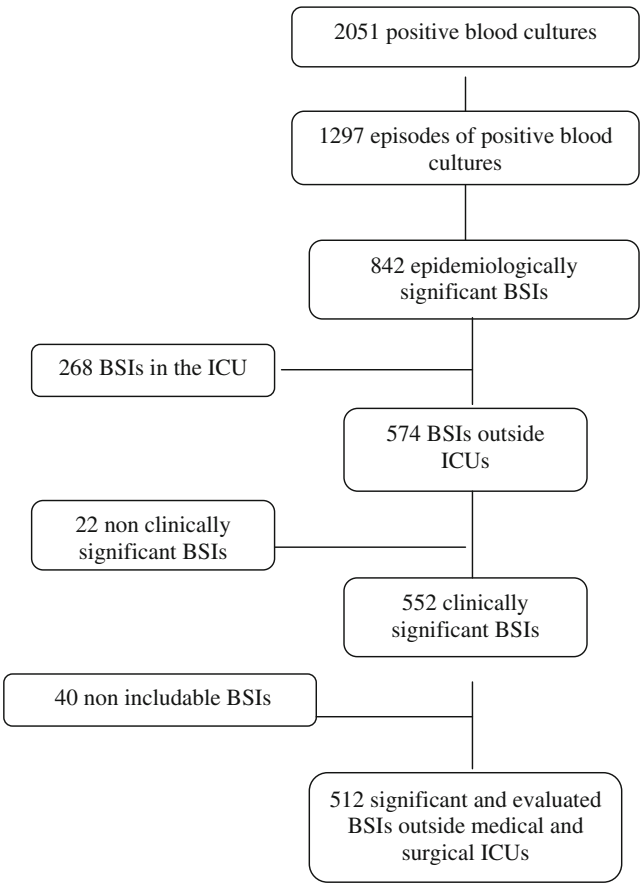

Fig. 1 Flow chart of positive blood cultures, Bichat–Claude Bernard Hospital, January 2008 to June 2009

In the univariate analysis, variables associated with an inappropriate or missing antibiotic therapy were underlying diseases fatal within 5 years: a healthcare-associated BSI, a BSI originating from a catheter or a skin and soft tissue infection, a BSI with Gram-positive cocci readily detectable upon direct examination of the positive BC, and a BSI due to multiply resistant bacteria. In the multivariate analyses, two variables were independently associated with an inappropriate or missing antibiotic therapy, a healthcare-associated BSI (adjusted odds ratio (aOR), 2.14; 95% confidence interval (CI), 1.46–3.13, $p<0.0001$), and a catheter-related BSI (aOR, 2.00; 95% CI, 1.09–3.66; $p=0.02$).

Discussion

Our surveillance showed that only 42.8% of antibiotic therapy for BSIs was appropriate at the time of the AMT intervention. Furthermore, antibiotic therapy was ineffective or missing in nearly 31% of cases involving BSIs, despite the rapid and direct communication of the positive BC results by the Bacteriology Laboratory, and the immediate availability of these results on the hospital's computerized patient data system. Although the initial aim of this study was not to assess the impact of the AMT, our results clearly demonstrate the importance of AMT intervention in starting and/or correcting the course of ongoing early empirical antibiotic therapies [5]. Early antibiotic therapy in septic patients with severe infections is critical in view of the demonstrated negative impact of delayed antibiotic treatment on the prognosis [7–9, 13–16]. However, the low rate of appropriate antibiotic therapy observed in this study (42.8%) might be an underestimation, since AMT intervention usually occurred early and within hours of positive BC results transmittal. Indeed, appropriate antibiotic therapy could very well have been started by the ward physicians within the following hours without any AMT intervention.

The independent risk factors for inappropriate or absent antibiotic therapy were a healthcare-associated BSI and a catheter-related BSI. That healthcare-associated BSI was a risk factor for inappropriate antibiotic therapy has been previously established [7] and is, therefore, not surprising. Nosocomial or healthcare-associated infections are usually more complex and involve microorganisms exhibiting an ever widening spectrum of resistance to common antimicrobials. Furthermore, except in rare cases such as that of ventilator-associated pneumonia, appropriate guidelines in dealing with these healthcare-associated BSIs are mostly lacking. Our results clearly support the idea that AMTs

Table 1 Variables associated with inappropriate antibiotic therapy before antibiotic management team (AMT) intervention

	Antibiotic therapy		RR	95% CI	*p*-value
	Appropriate (*n*=219)	Inappropriate/absent (*n*=293)			
Age (mean±SD, median)	61±21	64±18			0.08
Male gender (*n* [%])	110 (50)	173 (59)	1.16	0.99–1.36	0.02
McCabe score					
0 (ref)	109 (40)	101 (35)	1		
1	67 (30)	111 (38)	1.29	1.08–1.55	0.003
2	43 (20)	81 (27)	1.35	1.12–1.64	0.001
Clinical unit (*n* [%])					
Emergency room	17 (8)	34 (11)			NS
Medicine	160 (73)	190 (65)			
Surgery	42 (19)	69 (24)			
Type of BSI (*n* [%])					
Community-acquired (ref)	127 (58)	104 (35)	1		
Nosocomial	71 (32)	135 (46)	1.45	1.22–1.73	<0.0001
Healthcare-associated	21 (10)	54 (18)	1.59	1.30–1.95	<0.0001
Source of BSI					
Urinary (ref)	77 (35)	68 (23)	1		
Catheter	17 (8)	58 (20)	1.64	1.33–2.03	<0.0001
Digestive	33 (15)	45 (15)	1.23	0.95–1.59	NS
Pulmonary	27 (12)	19 (6)	0.88	0.59–1.29	NS
SSTI	15 (7)	26 (9)	1.35	1.01–1.80	0.03
SSI	16 (7)	22 (8)	1.23	0.89–1.70	NS
Other	34 (16)	55 (19)	1.31	1.03–1.67	0.01
Smear examination					
Gram-negative bacilli (ref)	115 (53)	110 (37)			1
Gram-positive cocci	78 (36)	142 (48)	1.31	1.11–1.55	0.005
Polymicrobial	5 (2)	18 (6)	1.60	1.24–2.06	0.003
Other	21 (10)	23 (8)			
Microorganism (*n* [%])	224	312			
Staphylococcus aureus	30 (13)	57 (18)			
CNS	6 (3)	43 (14)			
Streptococcus spp.	37 (16)	38 (12)			
Enterococcus spp.	10 (5)	21 (7)			
E. coli	86 (38)	71 (23)			
Other Enterobacteriaceae	28 (12)	47 (15)			
Aerobic Gram-negative bacilli	11 (5)	11 (4)			
Other	16 (7)	24 (8)			
Multiply resistant bacteria (*n* [%])	18 (8)	54 (18)	1.38	1.17–1.61	0.0004

should intervene to help physicians better manage BSIs, and that healthcare-associated BSIs should be the priority targets of their intervention.

The other variable associated with inappropriate or absent antibiotic therapy was a BSI with a catheter source. Most catheter-related infections outside the ICU stem from long-term central venous catheters, whose management remains problematic. Indeed, they often require a concomitant vancomycin therapy, for their underlying microorganism is the methicillin-resistant strain of *S. aureus* (MRSA) . In such situations, another central venous access is typically required, but dose adjustments remain complex [17]. The complex management of this infectious situation likely explains the low proportion (43%) of appropriate antibiotic therapy.

It is, therefore, critical that healthcare-associated and catheter-related BSIs are promptly identified. Most microbiology laboratories nowadays have access to computerized patient data showing the date and time a patient has entered the hospital, and the healthcare-associated nature of a BSI could often be inferred from the time elapsed between hospital entry and the onset of a bacteremia.

Here, it is worth noting that our study represents a nearly exhaustive evaluation by the AMT of BSI management within the hospital (in the medical and surgical ICUs, bacteriologists had daily meetings with the ICU staff, and were, therefore, not included in our present study). Furthermore, it is also worth pointing out the consistent and homogeneous pattern of AMT intervention throughout this study, since it took place almost systematically on the same day that the positive BC results were communicated.

However, our study probably has some minor limitations. Firstly, appropriate antibiotic therapy often started before the intervention and evaluation by the AMT physicians. A blind review by independent assessors would have limited the risk of observation bias. Secondly, the study was performed in a single hospital. Therefore, our results cannot be generalized because of potential effects of the local culture and habits on general practices and prescription guidelines. Although the impact of the AMT intervention on overall mortality was not evaluated, the death rate at day 30 was similar in both groups with or without appropriate antibiotic therapy. This can be explained by the fact that, in 93% of cases, AMT intervention was immediate, i.e., within hours of receiving positive BCs and evaluating the initially prescribed antibiotic therapy. Given the immediately apparent level of inefficacy (57.3%), our practice-based evidence study (which was part of everyday clinical practice) was not designed to be comparative as to include a control group not receiving AMT intervention.

The low rate of appropriate antibiotic therapy clearly supports an impact of the AMT in improving the management of antibiotic therapy in a hospital setting, and its intervention should preferentially focus on healthcare-associated BSIs.

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