**Factors influencing antimicrobial prescription attitudes in bloodstream infections: susceptibility results and beyond. An exploratory survey**

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**Background:** Novel rapid antimicrobial susceptibility testing (RAST) methods promise quicker de-escalation of broad-spectrum antibiotics. However, other behavioural and situational factors influencing antimicrobial prescription are not well known.

**Aim**: To explore factors associated with optimal antimicrobial prescription in patients with Gram-negative bloodstream infection and to propose specific scenarios in which a rapid antimicrobial susceptibility result may help to optimise prescribing.

**Methods**: exploratory survey (April-August 2018) in the UK and Spain using clinical case -related questions. Seniority, specialty and country of practice were recorded. Cases described patients with Gram-negative BSI, their empirical treatment and clinical course and the hypothetical RAST result. Respondents chose one of several options regarding antibiotic treatment management. Microbiologically optimal antibiotic choice (MOAC) was agreed by expert consensus beforehand. Responses were categorized as MOAC, request for support or sub-optimal choice. The relationship between the RAST result and the clinical course was defined as concordant (susceptible organism-clinical improvement; resistant organism-clinical deterioration) or as discordant otherwise.

**Findings:** 426 respondents **(**UK: 332; Spain: 94) and 1494 answers were analysed. Multivariate analysis identified that requests for support were 87% less likely in Spain; that antimicrobial resistance and clinical deterioration were associated with both increased request for support (OR 7.66 and OR 4.26 respectively) and MOAC (OR = 2.08 and OR = 2.06 respectively). A discordant clinical course was associated with 82% lower odds for MOAC. Out-of-hours results, seniority and specialty did not have an effect.

**Conclusion:** Antimicrobial choice is influenced by each country´s type of practice, clinical course and susceptibility results. Antimicrobial resistance was associated with increased optimal treatment, suggesting RAST may be less useful for step-down decisions in settings with low baseline resistance rates.

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**Introduction**

Bloodstream infection (BSI) is a main manifestation of sepsis and a major cause of morbidity and mortality across the world (1). Treatment recommendations for sepsis require rapid antibiotic treatment within an hour, so antibiotic treatment choice is made before results of antimicrobial susceptibility testing (AST) are available. Appropriate antibiotic choice is a balance between patients benefitting from rapid therapy with an effective agent and resistance-selection implications of prescribing unnecessary broad-spectrum antibiotics (2). Up to 50% of hospital antibiotic prescriptions may be inappropriate (3) and up to one-third of patients with BSI are treated with incorrect antibiotics while awaiting blood culture results (4). Improving antibiotic prescribing practices in hospitals is a priority in order to control the emergence and dissemination of resistant organisms(5).

Results from routine diagnostic laboratories, including microorganism identification and *in vitro* AST, provide guidance to clinicians in selecting appropriate antimicrobial treatments (6). . However, routine AST results take up to 4 days, which means that empirical antibiotic prescriptions are based on previous known local susceptibility results and the clinical presentation. Given the potential devastating effects of sepsis, empiric therapy tends to be with broad-spectrum antibiotics.

For these reasons, the development of rapid susceptibility testing (RAST) technologies are a high research priority in order to improve antibiotic use and reduce antibiotic resistance (7) (8) (9). These methods can provide susceptibility results within few hours after a positive culture (10). In clinical practice, the use of RAST has demonstrated to improve outcomes such as time to effective antibiotic and length of stay, but this is not consistent across the studies and seems to happen only in the presence of other interventions, such antimicrobial stewardship programs (11). This may suggest that perceptions and behaviors not related with diagnostic results may influence prescribing, and that perhaps a universal use of RAST may be neither necessary nor cost-effective. The impact of the implementation of RAST on antibiotic prescribing or patient outcomes is not well described.

Many complex factors other than AST results may determine antibiotic use (11), which has led to calls for research on behavioral and cultural aspects of antimicrobial usage with the aim to promote appropriate antibiotic therapy (9) (12). Research on antimicrobial prescription behavior has been done to understand prescribing for empiric therapy in situations where laboratory results are unavailable (13).

Individual prescription decisions may be based on many factors such as guidelines, literature review, personal experience or instructions passed down from senior colleagues. Ineffective communication of results between microbiology laboratory and clinicians may lead to inappropriate antimicrobial therapy choice (14).

This study used four clinical case-based scenarios histories To explore factors associated with optimal antimicrobial prescription in patients with Gram-negative bloodstream infection and to propose specific scenarios in which a rapid antimicrobial susceptibility result may help to optimise prescribing.

**Materials and Methods**

**Study design**

This descriptive, cross-sectional study was a web-based survey distributed to physicians of different specialities including internal medicine, emergency medicine, family medicine (general practice), geriatrics, paediatrics, infectious diseases/ medical microbiology, intensive care, general and orthopaedic surgery at a variety of secondary and tertiary hospitals across the United Kingdom and Spain. Participants were invited from two countries in order to find any differences in practice between two different health systems. Spain and the UK were chosen as the investigators had contacts in those countries and participants were mainly identified among investigator´s colleagues and contacts who cascaded to their respective contacts.

The main questionnaire (Survey Antimicrobial Prescription) was created using the online tool Survey Monkey ™ (15) by three of the authors, a team of UK-based infection physicians of whom two have also experience working in Spain. The 15 minutes-long survey consisted of eight items (four questions about the respondent on: position/role, specialty, years of experience and country/hospital of practice; four clinical case-based scenarios providing clinical and laboratory information - including RAST results - with questions about further antimicrobial treatment. English and Spanish versions were used for the UK and Spain, respectively. The survey is available in the Supplementary material (S1) and in the link <https://www.surveymonkey.co.uk/r/RM6VMPC>. The 4 case scenarios characteristics are summarised in **Figure 1.**

**Survey distribution**

Invitations to participate with the link to the online Antimicrobial User Survey were emailed initially to three of the authors´ professional contacts and relevant networks, encouraging the recipients to cascade to their own networks, without limitations in terms of specialty or role. The distribution was not limited to personal contacts only but included professional/institutional email distribution lists, at the discretion of the senders. The aim was to reach a variety of antimicrobial prescribers with different roles and seniority. Emails were sent to the relevant professional email addresses between April 2018 and August 2018 and collected within 5 months of the initial submission. Survey was closed on 31st December 2018. Participation was voluntary, non-remunerated and responses were anonymous. The respondents were asked to participate only once and the link to the survey was disabled after one use.

**Variables and definitions**

Medical specialties /departments were classified as either medical specialty (internal medicine; family medicine/general practice; emergency medicine; intensive medicine; geriatrics; pediatrics; infectious diseases/ medical microbiology) or surgical specialty (general surgery; trauma/ orthopedics; other surgical specialties).

The number or years practicing medicine from graduation were categorized as: <4 years; 4-8 years and >8 years. The length of specialty training and the speed in the acquisition of senior decision-making position/roles are notably different in the UK (2-year long foundation program [FY1-2] followed by up to 9 years of specialty training [ST1-9]) and in Spain (up to 5 years, R1-5) before reaching the senior specialist role (consultant and *adjunto* in the versions for the UK and Spain respectively). The positions/roles collected were standardized across both countries´ surveys in three categories, based on the equivalent independence and seniority in decision making and antimicrobial prescribing, as follows: category 1: consultant (*adjunto* in Spain) ; category 2: ST3-ST6 and above (R4-R5 in Spain) and category 3: FY1/FY2-ST1/ST2 (R1-R2-R3 in Spain). For analysis, these were re-grouped as senior position (category 1 or 2) or junior (category 3). Out-of-working hours (OOWH) was defined as the period of time between 5PM to 9 PM.

**Clinical case- based scenarios**

All four clinical case scenarios represented patients with common Gram-negative BSI presentations with different degrees of severity and evolving clinical conditions who were treated with an initial empiric (before susceptibility results were known) parenteral antibiotic. Each clinical case was designed to mimic a situation where a RAST result was given 12-36 hours after the initial presentation (when blood cultures were supposedly drawn). The scenarios all simulated reporting the results at different times in the day, two of them (Cases 2 and 3) OOWH.

Respondents were asked to select an antibiotic management choice based on both susceptibility results and the evolution of the clinical condition. The options given included request for support (deferring decision, discussion with other colleagues, await to next ward round, discussion with microbiology/infection team or with consultant/senior member of the team), antibiotic escalation and de-escalation options including intravenous (IV) and oral options. Respondents had to choose one single answer to each question. This was to try to capture 1) what action the treating physicians would prioritise and 2) how empowered they feel to make decisions around antimicrobial management when receiving results from the laboratory, while acknowledging that in real life often several actions happen at the same time.

In two out of four scenarios (case 1 and 4) the patient’s clinical condition improved after empiric therapy and in two scenarios (case 2 and 3) their clinical condition deteriorated. In two of the four scenarios (case 1 and 3) the isolate was reported as susceptible *in vitro* to the empiric antibiotic therapy, and in the other two (case 2 and 4) it was resistant. This means that in two scenarios the clinical course was discordant with the appropriateness of the empirical antimicrobial treatment given (susceptible isolate-clinical deterioration or resistant isolate- clinical improvement and in the other two, concordant (susceptible isolate-improvement or resistant isolate – deterioration). The key features, clinical and microbiological characteristics of each case scenario are shown in **Figure 1 and Supplementary material.**

An empiric antibiotic was defined as appropriate or inappropriate on the basis of whether the organism was reported *in vitro* susceptible to it.

Each of the answers were later categorized for the analyses as “microbiologically optimal” or “microbiologically sub-optimal” if in agreement with predefined expert-based criteria. Within the “sub-optimal” answers, there was a sub-category defined as “request for support”.

**Delphi survey of Microbiologically Optimal Antibiotic Choice (MOAC)**

The consensus on the optimal response from the antibiotic choice point of view to each question was decided using a Delphi survey-type of questionnaire (16) delivered also using SurveyMonkey ™ and called Expert survey) conducted beforehand among 15 (12 UK-based, 3 Spain-based) senior Infectious diseases/Medical Microbiology specialists . The antibiotic spectrum (broad vs narrow) was pre-defined for betalactam and non-betalactam antibiotics, modified from (17) (Supplementary material **Table 5).** The questionnaire is available through the link https://www.surveymonkey.co.uk/r/BQ6C8MD and in the Supplementary material.

For each clinical case, the experts were asked to categorise each of the possible answers as MOAC on the basis of the clinical details and the *in vitro* susceptibility results provided. An answer was considered to have met Delphi consensus when at least 75% of the experts agreed on it belonging to the “optimal” category (18) . Supplementary material Table 6 shows the answers considered to be MOAC as per expert consensus.

**Ethical approval**

All cases were hypothetical and contained no details of real patients. No identifiable details of respondents to the surveys were collected as a part of this survey. This study did not require ethics approval as per NIHR guidelines and our Institution´s research policies.

**Statistical analysis**

Descriptive statistics were used to summarize the survey answers. In this context, p values of ≤ 0.05 must be interpreted cautiously as potentially statistically significant. The individual abilities by the respondent to select an optimal choice, effective sub-optimal *in vitro* choice, (if the organism was sensitive *in vitro* to the antibiotic, but the choice was considered sub-optimal) or support request were calculated as percentages over the total number of valid answers given by that respondent (for example, if a respondent had selected a valid answer in all 4 cases and had selected 2 MOAC; 1 effective sub-optimal *in vitro* choice and 1 request for support choice, the individual percentage of MOAC was 2/4\*100 = 50%). The individual percentage of MOAC were compared by specialty, seniority and country. Aggregated percentages of each type of response per case were also calculated (for example, the aggregated percentage of MOAC for Case 1 was calculated as the number of times that all respondents had selected a MOAC option for that case by divided by the total number of valid answers (addition of MOAC, sub-optimal, optimal) by all respondents. These aggregated percentages were compared by susceptibility groups, concordance of clinical course (susceptible organism-clinical improvement; resistant organism-clinical deterioration), clinical severity (well/unwell) and out-of-hours group

Multinomial logistic regression was used to build a model to explore what factors may influence the type of antimicrobial choice. The unit of analysis was the answer provided to each case by each participant; the dependant variable was the antimicrobial choice, analysed as in three categories (effective sub-optimal *in vitro,* support request and optimal choice/MOAC) using the first as a reference category; The output is expressed as OR (95% CI) and shown as two separate regressions showing the effect of the variables in the final model on the odds for 1) requesting support and 2) selecting the microbiologically optimal choice, both as compared with the same reference category (effective sub-optimal *in vitro* choice). Statistical analyses were conducted in IBM SPSS Statistics for Windows, Version 21.0 (19).

**Results**

**Participants´ characteristics**

Responses were obtained from a total of 426 participants, 332 (78%) in the UK and 94 (22%) in Spain. Most of the participants were from medical specialties (370 vs 56). (**Table 1**). The mean time to complete the survey was 13 minutes. The median (IQR) individual percentages for optimal choice, request for support and sub-optimal choice were 50% (33, 75); 25 % (0,50) and 25 % (0,50) respectively.

Compared to Spain, in the UK there were significantly more respondents in the intermediate position category of seniority (ST3-6 or equivalent) (73/332 [22%] vs 9/94 [10%]) and fewer consultants or equivalent (182/332 [55%] vs 60/94 [64%], (p = 0.026), as shown in Table 1. When regrouped in two categories as described in the methods section, the proportion of respondents in senior positions were similar in both countries (255/332[77%] in the UK vs 69/94 [73%] in Spain, p 0.495).

**Clinical case-based scenarios answers**

The number of missing answers ranged from 36 to 67 (8% to 16%) of the respondents depending on the case. Among the valid answers to each scenario, MOAC were given in 289/390 (74%) and 251/377 (67%), for cases 1 and 2, with concordant clinical course compared to 147/368 (40%) and 119/359 (33%), for cases 3 and 4, with discordant clinical course (p for overall concordant vs discordant group comparison <0.001). Support was requested by 18 (5%), 109 (29%), 108 (29%) and 149 (42%) for cases 1 to 4 respectively **(Figure 2).**

**Differences in the type of answer by country, specialty and seniority**

Overall, in the univariate analysis, there were statistically more MOAC among respondents from Spain, with significantly higher requests for support amongst the participants from the UK **(Table 2)**. Respondents from medical specialties were more likely to give a MOAC, and respondents from surgical specialties more likely to request support. There were no overall differences in the type of response given by seniors as compared with juniors. Overall, the specialties requesting support more often (expressed as mean %) were: general surgery (36% of respondents) and other surgical specialties (35%), emergency medicine (33%), paediatrics (32%), orthopaedic surgery (30%), geriatrics (29%), intensive medicine (25%), infectious diseases/microbiology (21%), internal medicine (20%), family medicine (13%). The sub-analysis by country showed that the request for support was much less common among the Spanish respondents and recorded in fewer specialties (family medicine = 14%; general surgery = 8%, internal medicine = 6%, geriatrics = 5%, paediatrics = 4%; not recorded for the rest of specialties).

**Influence of the case characteristics in the choice of the answer**

1494 answers from 426 respondents were analyzed (Table 3) The percentage of answers selecting a MOAC was higher in Cases 1 and 2, compared to that of 3 and 4, and the percentage of support request was much lower in Case 1 compared to the other cases. Responses to cases with discordant clinical course were less often a MOAC, and more often sub-optimal/requests for support, when compared with those with concordant clinical course. The proportion of requests for support was significantly higher when the isolate was resistant, there was clinical discordance, the patient was unwell or the result was given out of working hours.

The adjusted odds ratios for requesting support were significantly lower, 87% less, among responses from Spain-based participants; nearly eight times higher if the isolate was resistant to antimicrobials and four times higher if the patient was clinically unwell. Responses from senior doctors were associated with 30% reduction in the odds for request for support, but this was non-statistically significant. The odds for choosing an optimal antimicrobial choice were reduced by 82% when there was a discordant clinical course. A resistant isolate or clinical deterioration increased both the odds for requesting support (nearly eight and four times higher respectively) and for choosing an optimal antimicrobial choice (two times higher in both cases). Neither the country of origin of the respondents nor the seniority or specialty had an influence on the antimicrobial choice after adjusting for other variables in the model (**Table 4)**.

**Discussion**

To our knowledge, this is the first survey study to investigate antimicrobial prescription attitudes that incorporates the value of the microbiological information provided by RAST methods for the management of BSI, based on different realistic clinical scenarios.

The development of rapid diagnostic devices for *in vitro* antibiotic sensitivity testing is one of the key components of policies aiming to improve outcomes and reduce antibiotic resistance (9). However, if the mechanisms behind prescribing attitudes are not fully understood, simply introducing a rapid diagnostic test is unlikely to change patient management.

In a recent survey study based on simple general questions, most respondents (83%) said they would change empirical antimicrobial therapy (83%) and narrow the antimicrobial spectrum (78%) based on RAST results in patients with BSI (4). These findings suggest that shortening the turn-around time of positive blood culture identification and susceptibility results could optimise antimicrobial treatment in those patients. However, our study suggests that the result of an *in vitro* antibiotic sensitivity testing is likely not the only determinant of the choice of antibiotic treatment. We identified potential important determinants of antibiotic choice, which can be patient/case-related, prescriber-related and situational/country-related factors.

In this study, cases with discordant clinical course were associated in the adjusted analysis with lower likelihood of an optimal antimicrobial choice. This makes sense intuitively and has been described elsewhere (20). An example of this could be, patients with BSI with known *in vitro* susceptible organisms but who are unwell are either kept on broad-spectrum antibiotic or escalated to even broader-spectrum antibiotics, neither of which option is MOAC. The influence of the culture of treating sepsis aggressively, fear of blame and management/avoidance of uncertainty has been described in recent work on antimicrobial behavior ~~based in London~~ (12), (21).

Lack of understanding of the microbiology laboratory processes involved, mistrust in new technologies and difficulties assessing the benefits of new technologies against more traditional tests may be important in these situations and have been identified as barriers to implementation of new technologies (22). The prescribing etiquette or avoidance to alter other prescriber’s decisions based on respect for another’s clinician’s clinical judgement (23) could also explain some of the differences.

Antimicrobial resistance and clinical deterioration were associated with both request for support and optimal antimicrobial choice. The fact that, in our study, antimicrobial resistance is associated with selection of MOAC could be an indicator that this is the group of patients that may benefit the most from the implementation of RAST methods in routine practice. This finding suggests that RAST may be less useful for step-down decisions in settings with low baseline resistance rates. It is plausible and logical that in the two cases (cases 2 and 4) where the patient had BSI by a resistant isolate, the escalation to a broader, appropriate antimicrobials was driven by the susceptibility result provided. This could potentially mean that the treating teams pay more attention to the drug chart and the antimicrobial treatment when a report suggesting a resistant isolate is issued, and perhaps less when the isolate is susceptible. Theoretically, an earlier escalation to the broader-spectrum antibiotic facilitated by a rapid result could have prognostic implications. Conversely, in settings with lower resistance rates, the cost of implementing a RAST may not be justified.

The apparent differences between countries observed in the univariate analysis shown in Table 2 (i.e. Spain-based respondents had a higher frequency of MOAC) were not confirmed in the multivariate analysis; these differences seemed to be mainly driven by differences in the request for support (much higher among the UK-based respondents). In the multinomial logistic regression analysis, which is the appropriate for outcomes with three categories, the country was associated with the request for support, but not with the choice of the MOAC. This and the different distribution of specialties largely reflects the structure of the infection specialty and the type of work the specialists dealing with infections do in both countries. In the UK, there is near universal availability of in and out of hours clinical microbiologist advice on antimicrobial prescription, which is widely used by medical and surgical teams to discuss antimicrobial choices with infection specialists; this resource is less frequently used routinely in Spain, other than for more complex infections requiring an ad-hoc referral for review during working hours by the infection specialist. In Spain, out of hours, the parent teams tend to manage the antimicrobial prescription decisions themselves, as the out of hours support by ward-based infection specialists is not universal and centre-dependent. In the UK, the type of consultation that the infection specialists offer for patients with BSI is predictable and more standardised across the nations, and perceived by the rest of the teams as a “support service” that is available and can be requested (shared medical responsibility & prescription culture). In Spain, although in practice the same type of advice is provided, it may not be perceived as support but rather as an independent activity initiated by the infection team themselves, and the prescribers may feel less *policed* and more free to decide independently which antimicrobial changes to make. There are well established antimicrobial stewardship programs (AMS) and national resistant reduction plans in both Spain and the UK (24). The structure and function of the role of the AMS teams is similar in both countries, so this not necessarily justify differences found with regards prescription behaviour. In Spain, as in the UK, the AMS teams do not normally intervene in the choice of the initial antimicrobial treatment. The 24-hour advice available in the UK is probably the reason for the differences observed between countries with regards requesting support.

 A limitation of the study was the distribution of the survey as selection and distribution was not systematic. This could have introduced sample selection and response bias, however the relatively large number of participants across a number of specialties should reduce this risk. The number of centres/departments surveyed was limited and may not be representative of the wider population in either country. Another possible limitation may have been the fact that only clinicians who were confident in prescribing antibiotics responded the survey, which may have resulted in a sample bias.

The artificially created clinical scenarios were representative of commonly encountered cases in the clinical practice. However, it is very difficult to translate the complexities of decision making in a survey format and direct extrapolation of the results should be interpreted with some caution. For example, in real life it is common to take an antimicrobial decision and request support at the same time, but our survey only allowed to select one of three mutually exclusive options. The final model fit well the data (p < 0.001) but the model predicted only about a third of the variability of the data (Nagelkerke pseudo R2= 0.286), suggesting that there are other variables not captured by the model that further explain antimicrobial prescription attitudes. The study was not powered, although the number of valid responses was high enough (N = 1494) to detect important effects. Finally, the cases were limited to patients with invasive Gram-negative infection and may not be generalizable to other clinical situations.

**Conclusion**

Our study suggests that there are both patient/case-related (antimicrobial resistance, clinical presentation, clinical discordance) and prescriber/situation-related factors (country) that determine antibiotic prescription which are unrelated to the results of RAST. Rapid antimicrobial susceptibility testing methods may have an important role in reducing the time to appropriate antimicrobial, however, these may not be realised in practice unless the other factors determining antibiotic choice in the patient pathway are better understood. Further research in antibiotic choice is needed to confirm these results and to optimise the use of RAST methods.

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