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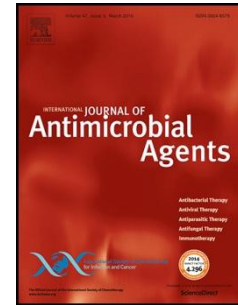
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**1 SHORT COMMUNICATION****2 Management of bloodstream infections by infection specialists: an international****3 ESCMID cross-sectional survey**

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34

35 **Running title:** Bloodstream infections' survey

36

37 Word count: 2249/2500

38 2/3 tables, 16/20 references, 6 supplemental files

39

40

#### 41 **Highlights**

- 42 • We noted important variations in management of bloodstream infections.
- 43 • Management was often not compliant with IDSA guidelines.
- 44 • Compliance with guidelines was better among antimicrobial stewardship team members.

45

46

47

48 **ABSTRACT (247/250 words)**

49 **Background.** Bloodstream infections (BSI) are frequent, but international guidelines are available  
50 only for MRSA and candidaemia.

51 **Objectives.** Our objective was to explore the management of BSI by infection specialists.

52 **Methods.** This international ESCMID cross-sectional survey was opened from December 2016 to  
53 February 2017. All infection specialists, senior or trainees, giving at least weekly advice on positive  
54 blood cultures could participate. Their practices were evaluated using six clinical vignettes  
55 presenting uncomplicated BSI cases.

56 **Results.** Six hundred and sixteen professionals from 56 countries participated (333/616, 54%  
57 infectious diseases specialists, 188/616, 30% clinical microbiologists), 76% (468/616) being  
58 members of an antimicrobial stewardship team. Large variations in practice were noted, in  
59 particular for the *E. coli*, *E. faecalis* and *P. aeruginosa* vignettes. Echocardiography was considered  
60 standard of care by 81% (373/459) of participants for MRSA, 78% (400/510) for MSSA and 60%  
61 (236/395) for *C. albicans*. Antimicrobial combination therapy was recommended by 2% (8/360) of  
62 the respondents for *C. albicans*, 11% (43/378) for *E. coli*, 27% (114/420) for MRSA and 39%  
63 (155/393) for *E. faecalis*. IV-oral switch was considered in 68% (285/418) for MRSA, 79%  
64 (306/388) for *E. faecalis*, 72% (264/366) for *P. aeruginosa* and 75% (270/362) for *C. albicans*. In  
65 multivariable analysis, IDSA guideline-compliant practice was more frequent among participants  
66 belonging to an antimicrobial stewardship team (aOR 1.7, p=0.018 for the MRSA vignette and aOR  
67 2.0, p=0.008 for the candidaemia one).

68 **Conclusion.** Our survey showed large variations in practice among infection specialists.  
69 International guidelines on management of BSI are urgently needed.

70

71 **Keywords:** antibiotic stewardship; bacteraemia; blood culture; candidaemia; questionnaire; survey

72

**73 1. INTRODUCTION**

74 Bloodstream infections (BSI) are frequent in hospitalised patients, and are associated with  
75 significant morbidity and mortality [1]. Expert advice from an infection specialist is associated with  
76 better outcomes, in particular for *Staphylococcus aureus* bacteraemia and candidaemia [2-5]. Many  
77 infectious disease (ID) consultation services and hospital-based antimicrobial stewardship (AMS)  
78 teams include expert advice for (some or all) positive blood cultures in their programme [6]. It is  
79 essential that recommendations made by these experts to prescribers are consistent, and evidence-  
80 based [2].

81 Blood cultures coming back positive in a patient without any source of infection identified  
82 yet is a situation encountered every day by ID physicians and AMS teams. Only few international  
83 guidelines, however, address BSI, in particular if not clearly related and secondary to organ  
84 infection such as pyelonephritis, pneumonia, or abdominal infections. To the best of our knowledge,  
85 for the other (primary) BSI cases, only MRSA and *Candida* are covered by international guidelines,  
86 the most recent ones being the Infectious Diseases Society of America (IDSA) 2011 and 2016 ones  
87 respectively [7,8]. Management of catheter-related BSI is also partially covered by the 2009 IDSA  
88 guidelines [9]. Lack of guidelines might lead to wide variations in practice and to practices that  
89 might deviate from published evidence.

90 The aim of our survey was to explore variations in the management of patients with BSI by  
91 infection specialists and to identify demographic and professional individual characteristics  
92 associated with IDSA guideline-compliant management of MRSA bacteraemia and candidaemia.

93

## 94 2. MATERIAL AND METHODS

### 95 2.1. Study design

96 ESGAP (ESCMID Study Group for Antimicrobial stewardshiP) and ESGBIS (ESCMID  
97 Study Group for Bloodstream Infections and Sepsis) conducted an exploratory cross-sectional  
98 international survey on management of bloodstream infections. It was self-administered and  
99 internet-based, using SurveyMonkey® (Palo Alto, California, USA) software. Hospital-based  
100 healthcare professionals (fully trained or in training) who were giving at least weekly advice to  
101 colleagues (outside their home department) on their antibiotic prescriptions for positive blood  
102 cultures could participate in this survey.

103

### 104 2.2. Survey instrument

105 The 43-item questionnaire was developed by a multidisciplinary group of experts in  
106 infectious diseases (ID), clinical microbiology (CM) and public health, based on a literature review  
107 (Appendix A) [9-12]. It was first pilot-tested among ESGAP and ESGBIS Executive Committee  
108 members to check for clarity and conciseness.

109 The questionnaire (Appendix B) had three parts: (i) respondent's characteristics; (ii)  
110 organization of care regarding bloodstream infections in the respondent's hospital; and (iii) usual  
111 management of bloodstream infections by the respondent using six clinical vignettes. All the  
112 vignettes presented an immunocompetent 85-kg male patient without (severe) sepsis or septic  
113 shock, with a normal renal function, no comorbidity and no allergy. We assumed a 'best-case  
114 scenario', meaning that clinical outcome was rapidly favourable under the antimicrobial treatment.  
115 There was no risk factor for infective endocarditis and no implantable material in place. The six  
116 vignettes differed according to the isolated pathogen: methicillin-susceptible *Staphylococcus aureus*  
117 (MSSA), MRSA, *Enterococcus faecalis*, ESBL-producing *Escherichia coli*, *Pseudomonas*  
118 *aeruginosa*, and *Candida albicans*. Susceptibility testing results were detailed for each isolate.  
119 There was no obvious primary or secondary focus of infection upon initial clinical examination,

120 except for the *P. aeruginosa* and *C. albicans* vignettes, where the infection was hospital-acquired  
121 and catheter-related, with the vascular catheter being quickly removed. For each vignette, the  
122 respondent was asked about: (i) the investigations s/he would systematically perform in search of  
123 complication or source of infection; (ii) the antimicrobial molecule(s) used as first-line targeted  
124 therapy, as single or combination treatment; (iii) the total daily dose, the route of administration,  
125 and the total duration of treatment; and (iv) if s/he would plan follow-up blood cultures at 48-72  
126 hours, and if an IV-oral switch would be considered.

127

### 128 2.3. Survey distribution

129 The survey stayed open from the 1<sup>st</sup> of December 2016 to the 28<sup>th</sup> of February 2017, with  
130 one reminder sent one month before closure. It was advertised using the ESCMID Newsletter, as  
131 well as ESGAP and ESGBIS networks. Participation was voluntary, anonymous and without any  
132 compensation. Anonymity was guaranteed at all phases of data collection and analyses. Ethical  
133 approval was not required.

134

### 135 2.4. Statistical analyses

136 Participants' demographic and professional characteristics, as well as their hospital's  
137 organisation of care concerning the management of BSI were described as numbers and  
138 percentages. Responses on the management (investigations, antibiotic therapy, follow-up blood  
139 cultures, IV-oral switch, and duration of treatment) of each clinical vignette were also presented as  
140 numbers and percentages.

141 Demographic and professional characteristics associated with IDSA guideline-compliant  
142 management of MRSA bacteraemia and candidaemia were identified using bivariate and  
143 multivariable logistic regression models. Eight variables, related to the respondent and hospital  
144 characteristics, were a priori selected to be included as explanatory variables in the models  
145 (Appendixes E and F). IDSA guideline-compliant management was defined as responses compliant



146 with the IDSA guidelines [7,8] (Appendix A) concerning (i) the chosen treatment (single therapy  
147 with vancomycin or daptomycin for MRSA, an echinocandin or fluconazole for *Candida*); (ii) the  
148 investigation(s) (echocardiography for MRSA, fundus examination for *Candida*); (ii)  
149 recommendation of performing follow-up blood cultures; and (iv) the treatment duration (at least 14  
150 days from the first negative blood culture). For these three last criteria, management was still  
151 considered as IDSA guideline-compliant if a reply was missing for one criterion, or if one criterion  
152 did not comply with guidelines.

153 Explanatory variables reaching a threshold of  $p < 0.20$  in bivariate models were then entered  
154 in multivariable models, with  $p < 0.05$  being considered as significant using two-sided tests.  
155 Statistical analyses were performed using SAS® version 9.4 (SAS® Institute, Inc., Cary, N.C.).

## 156 3. RESULTS

### 157 3.1. Respondents' characteristics

158 Six hundred and sixteen professionals participated in this survey, coming from 56 countries  
159 (Appendix C), mainly Germany (21%, 125/595), France (12%, 71/595), Turkey (7%, 43/595), the  
160 United Kingdom (UK, 6%, 34/595), and Italy (5%, 31/595). Respondents' characteristics are  
161 detailed in Table 1.

162

### 163 3.2. Organisation of care regarding bloodstream infections

164 International guidelines on antimicrobial therapy for bacteraemia/candidaemia were the  
165 most accessible references for 66% of respondents (393/595), followed by national guidelines for  
166 53% (318/595), local ones for 51% (304/595), while 6% (36/595) declared not having access to  
167 guidelines in their hospital. When guidelines were accessible, they gave recommendations on the:  
168 (i) diagnostic work-up, for primary and secondary foci of infection, for 64% of the respondents  
169 (359/559); (ii) management according to the specific microorganism for 69% (387/559); (iii)  
170 empirical therapy choices according to the Gram stain for 44% (245/559), or according to the  
171 MALDI-TOF results for 15% (86/559); and (iv) targeted therapy choices for 62% (347/559). They  
172 also specified the choice of the antimicrobial agent for 76% (424/559), the dose for 73% (407/559),  
173 the route of administration for 72% (404/559) and the total duration of treatment for 66% (368/559).

174 Systematic expert advice to prescribers for positive blood cultures was in place for all  
175 positive cultures in 54% (300/551) of the cases and **in specific situations in 18% (99/551)**; the  
176 professional in charge for delivering advice was a member of the antimicrobial stewardship team  
177 for 46% of respondents (180/393), a senior infectious diseases specialist for 67% (263/393), a  
178 senior clinical microbiologist for 45% (176/393), a senior clinical pharmacist for 13% (49/393)  
179 and/or a trainee for 16% (64/393). The expert gave recommendations on the diagnostic work-up in  
180 94% of cases (372/395) and on the treatment in 84% (330/395). Systematic follow-up of the patient  
181 was planned in 62% (244/395) of the cases (68% (146/213) for ID and 55% (72/130) for CM). The

182 expert gave advice on the phone in 69% of the cases (272/395, 61% (131/213) for ID and 82%  
183 (107/130) for CM) and/or performed a bedside consultation in 72% (282/395, 80% (171/213) for ID  
184 and 62% (80/130) for CM).

185

### 186 3.3. Management of bloodstream infections

187 Results for each clinical vignette are detailed in Table 2, with Appendix D presenting  
188 additional findings. The proportion of respondents considering combination therapy was 20%  
189 (MSSA) and 27% (MRSA) for staphylococcal BSI, respectively, but otherwise ranged between 2%  
190 (for candidaemia) and 39% for enterococcal bacteremia. An early switch to oral therapy (after 48-72  
191 hours of therapy) was considered by 9% (MRSA) to 34% (ESBL-producing *E. coli*) of respondents,  
192 with few respondents (<30%) reporting oral therapy as inadequate for the different BSI. Most  
193 (>80%) respondents would ask for follow-up blood cultures in *S. aureus* BSI and candidaemia.

194

### 195 3.4. Factors associated with IDSA guideline-compliant management for the MRSA and *C. albicans* 196 vignettes

197 Around one third (30%, 185/616) of respondents advised an IDSA guideline-compliant  
198 management for the MRSA bacteraemia vignette. Giving advice on positive blood cultures at least  
199 daily vs at least weekly (aOR=1.5; p=0.025) and being a member of an antimicrobial stewardship  
200 team (aOR=1.7; p=0.018) were both independently associated with an IDSA guideline-compliant  
201 management in the multivariable analysis (Appendix E).

202 A quarter of the respondents (24%, 149/616) advised an IDSA guideline-compliant  
203 management for the *C. albicans* vignette. Individual characteristics independently associated with  
204 an IDSA guideline-compliant management in the multivariable analysis were: being an infectious  
205 diseases specialist (aOR=1 vs microbiologist aOR=0.5; pharmacist aOR=0.1; other medical  
206 specialist aOR=0.6; overall p=0.005); being a member of an antimicrobial stewardship team  
207 (aOR=2.0; p=0.008); age >30 years (30-50 years vs <30: aOR=2.9; >50 years vs <30: aOR=1.7;

208 overall  $p=0.027$ ); and practicing in a university public hospital (aOR=2.4 vs other public hospital  
209 aOR=1.6; private hospital aOR=1; overall  $p=0.024$ ) (Appendix F).

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**210 4. DISCUSSION**

211 Our large exploratory survey included more than 600 infection specialists, mostly (84%)  
212 CM or ID, members of an AMS team in 76% of the cases, coming from all continents. We noted  
213 important variations in management of bloodstream infections. Variation in practice and probably  
214 uncertainty among experts appeared to be relevant in therapy duration, drug dosing and time to IV-  
215 oral switch therapy, and that included *S. aureus* BSI. For the MRSA bacteraemia and candidaemia  
216 vignettes, management was compliant with IDSA guidelines in less than one third of the cases, and  
217 belonging to an AMS team was independently associated with more frequent guideline-compliant  
218 practice.

219 Respondents declared that BSI guidelines were available in 93% of the cases in their  
220 hospital. However, our results suggest that these guidelines could be optimised, since few provided  
221 all elements necessary to optimize BSI management; as an example, choosing empirical antibiotic  
222 therapy based on direct examination results was available in only half of the cases. Moreover,  
223 systematic expert advice for positive blood cultures was in place in only 54% of the hospitals.

224 Investigations looking for the source of infection or complications were highly variably  
225 used. For the *E. coli* and *E. faecalis* vignettes for example, urine cultures and abdominal imaging  
226 were requested quite infrequently, even though they are usually recommended in the literature  
227 [11,12]. Planning an evidence-based diagnostic work-up in case of BSI is however essential, and  
228 should ideally be part of AMS teams' activities, since it has a direct impact on source control and  
229 choice of the best antibiotic regimen.

230 Route of administration of antimicrobials showed similar variation between respondents.  
231 The majority considered an IV-oral switch for the *S. aureus* and *E. faecalis* vignettes, even though  
232 the 2011 IDSA MRSA guidelines do not recommend an oral treatment [7]. On the contrary, for the  
233 uncomplicated ESBL-producing *E. coli* primary bacteraemia, due to an isolate that was susceptible  
234 to cotrimoxazole, 27% never considered an IV-oral switch and only 6% initially started the patient  
235 on cotrimoxazole.

236 Durations of treatment were also quite long for most of the vignettes, as compared to  
237 available literature. French suggestions, based on a literature review, for uncomplicated primary  
238 bacteraemia are 7 days for Enterobacteriaceae and Enterococci, 10 days for non-fermentative Gram-  
239 negative bacilli and 14 days for *S. aureus* [10].

240 Finally, we found an unexpectedly low compliance rate with IDSA guidelines for the MRSA  
241 bacteraemia and candidaemia vignettes among the surveyed infection specialists. This was  
242 previously found for endocarditis [13,14]. This could be due to many factors [15], in particular: lack  
243 of agreement with the guidelines, especially on controversial topics not well supported by evidence;  
244 difficulty to adapt guidelines in complex patients; absence of update of guidelines; guidelines that  
245 are not easily generalisable to the country/setting of practice.

246 Our exploratory survey presents original findings, but has some limitations. It is possible  
247 that the most motivated or knowledgeable infection specialists participated, which might limit the  
248 generalisability of our results. The majority of participants also originated from a relatively small  
249 number of countries, and we cannot calculate response rates (overall or by country). We had  
250 missing data for some questions, but this is acknowledged in our presentation of the results. Finally,  
251 although vignettes have been shown to be a valid tool for assessing healthcare professionals'  
252 practices [17], responses may not necessarily reflect the daily practices of respondents. Moreover,  
253 by offering respondents to select answers they might have been more likely to say that they would  
254 carry out investigations that they would not do in routine practice.

255

## 256 CONCLUSIONS

257 Our survey shows that infection specialists manage BSI very differently and that  
258 organisation of care regarding management of BSI at hospital level could be improved. We feel that  
259 such large variations might be a threat to antimicrobial stewardship programmes, and could  
260 undermine the credibility of AMS team members among prescribers. International evidence-based  
261 guidelines on management of the most frequent BSI are urgently needed, with identification of the

262 priorities for future research due to lack of evidence. The ESCMID/IDSA guidelines on *S. aureus*  
263 bacteraemia and the ESCMID guidelines on multidrug-resistant Gram-negative bacteria that are  
264 currently under preparation are a step in that direction. National detailed guidelines should also be  
265 made available to prescribers, and implemented by AMS teams at local level. Uptake of these  
266 guidelines among infection specialists needs however to be planned beforehand, as well as a  
267 thorough evaluation of barriers and facilitators in case of low uptake.

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270

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273 not-for-profit sectors.

274

**275 ETHICAL APPROVAL**

276 Not required.

277

**278 TRANSPARENCY DECLARATION**

279 No conflict of interest to declare for all authors.

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281 **Table 1 – Respondents' characteristics (N=616)**

Characteristics	% (n/N)
Frequency of advice on antibiotic prescriptions for positive blood cultures	
At least daily	63 (388/616)
At least weekly	37 (228/616)
Main specialty	
Infectious diseases specialist	54 (333/616)
Clinical microbiologist	30 (188/616)
Clinical pharmacist	5 (27/616)
Other medical specialist	9 (56/616)
Other	2 (12/616)
Member of an antimicrobial stewardship team	
Yes	76 (468/616)
No	24 (148/616)
Gender	
Male	56 (337/597)
Female	44 (260/597)
Age	
< 30 years	5 (28/598)
30- 50 years	65 (389/598)
> 50 years	30 (181/598)
Type of hospital	
University public hospital centre	49 (291/599)
Other public hospital	33 (197/599)
Private hospital/clinic	14 (87/599)
Other	4 (24/599)
Years of practice	
I haven't started my specialty training yet	1 (8/599)
I am currently doing my specialty training	7 (40/599)
0 - 2 years	8 (46/599)
3 - 5 years	18 (108/599)
6 - 10 years	19 (114/599)
> 10 years	47 (283/599)

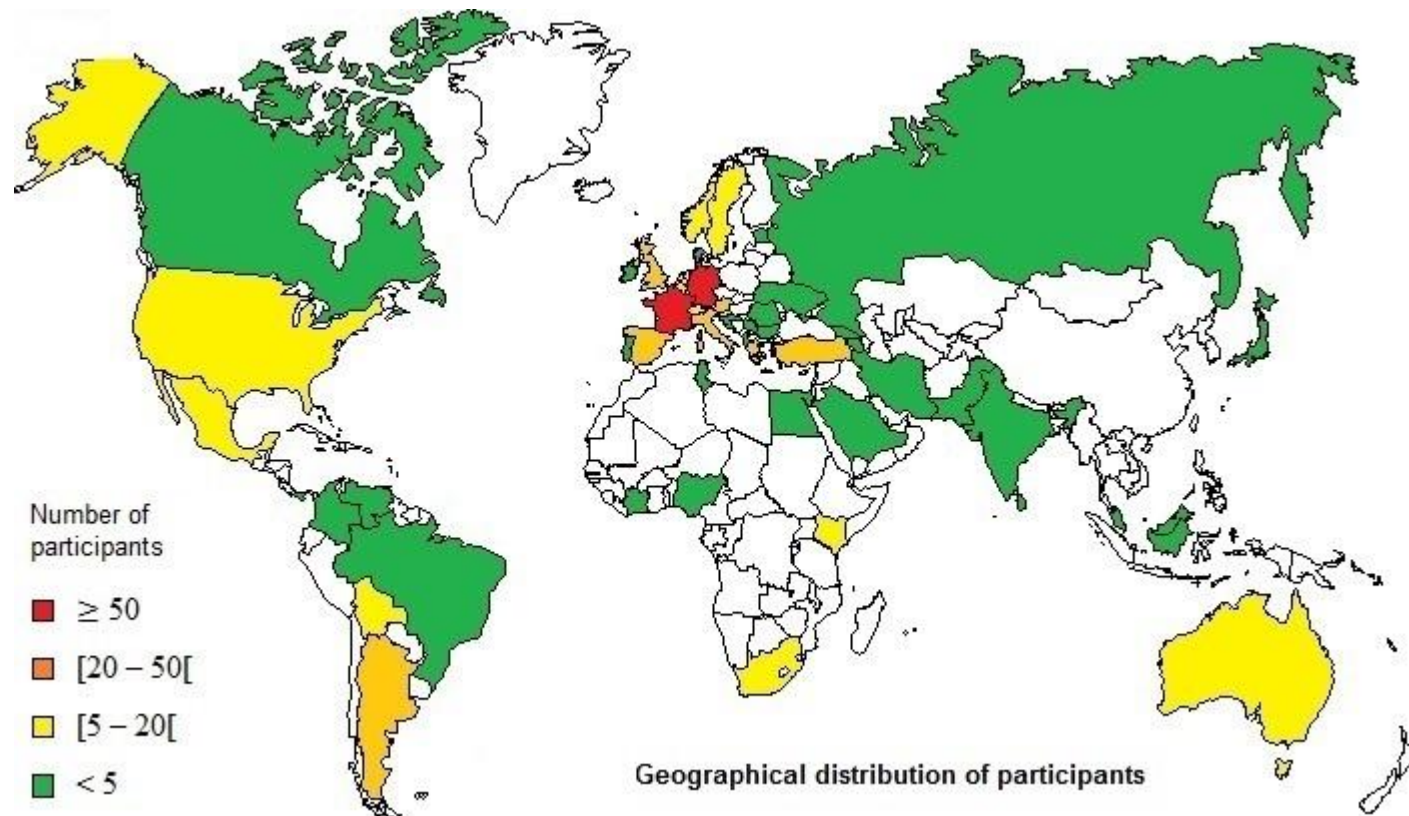
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283 **Table 2 – Management of bloodstream infections by the respondents in six clinical scenarios (N=616)**

	MSSA	MRSA	<i>E. faecalis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
<b>Investigations % (n/N)</b>						
Echocardiography	78 (400/510)	81 (373/459)	60 (262/438)	8 (34/418)	10 (40/418)	60 (236/395)
CT scan	11 (57/510)	13 (59/459)	14 (63/438)	14 (58/418)	8 (34/418)	12 (46/395)
Chest X-ray	8 (38/510)	7 (33/459)	2 (7/438)	5 (19/418)	11 (45/418)	3 (13/395)
Abdominal ultrasound	5 (27/510)	6 (28/459)	13 (58/438)	27 (114/418)	10 (40/418)	13 (50/395)
Urine culture	2 (11/510)	2 (11/459)	14 (62/438)	37 (154/418)	18 (72/418)	6 (22/395)
Colonoscopy	0 (0/510)	0 (0/459)	10 (42/438)	3 (13/418)	0 (1/418)	0 (1/395)
Fundus examination	3 (14/510)	3 (13/459)	1 (2/438)	0 (1/418)	0 (1/418)	44 (174/395)
Other	7 (33/310)	6 (29/459)	1 (5/438)	1 (3/418)	3 (12/418)	4 (17/395)
<b>Targeted antimicrobial therapy</b>						
Combination therapy % (n/N)	20 (87/440)	27 (114/420)	39 (155/393)	11 (43/378)	32 (119/365)	2 (8/360)
Most frequently prescribed antimicrobial	Anti-staphylococcal penicillins	Vancomycin	Amoxicillin/Ampicillin	Imipenem/Meropenem	Ceftazidime	Fluconazole
Most frequent daily dose (grams)	12	2	12	[2.5-4]	6	0.4
<b>Follow-up blood cultures % (n/N)</b>	83 (365/440)	86 (357/417)	64 (249/391)	39 (147/378)	48 (176/364)	90 (324/359)
<b>IV-oral switch % (n/N)</b>						
Yes after 48-72h of therapy	17 (73/438)	9 (38/418)	27 (105/388)	34 (129/378)	28 (103/366)	24 (86/362)
Yes after 10 days	26 (116/438)	25 (105/418)	23 (90/388)	18 (69/378)	23 (85/366)	34 (122/362)
Yes in specific situations	33 (146/438)	34 (142/418)	29 (111/388)	18 (70/378)	21 (76/366)	17 (62/362)
Never	23 (99/438)	32 (132/418)	21 (80/388)	27 (100/378)	26 (96/366)	17 (63/362)
Not applicable (already started an oral treatment)	1 (4/438)	0 (1/418)	1 (2/388)	3 (10/378)	2 (6/366)	8 (29/362)
<b>Duration of treatment (days)</b>						
Median	14	14	10	10	14	14
Q1-Q3	10-14	14-14	10-14	7-14	10-14	14-14
Mode (n/N)	14 (284/435)	14 (294/415)	14 (157/385)	10 (118/373)	14 (162/361)	14 (296/359)
Second mode (n/N)	10 (57/435)	10 (46/415)	10 (113/385)	7 (117/373)	10 (91/361)	21 (21/359)

284 Abbreviations: MSSA = Methicillin-susceptible *Staphylococcus aureus*, MRSA = Methicillin-resistant *Staphylococcus aureus*, CT = CT-scan, US =  
285 ultrasound, Q1 = first quartile, Q3 = third quartile

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Appendix C - Map\_V3.jpg