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Original Article

Fast track SSTI management program based on a rapid molecular test (GeneXpert® MRSA/SA SSTI) and antimicrobial stewardship

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Abstract *Purpose:* This study examines the impacts of a skin and soft tissue infection (SSTI) management program involving a rapid diagnostic algorithm (Gram stain plus real-time PCR, GeneXpert® MRSA/SA SSTI) performed directly on clinical samples plus antimicrobial stewardship (AMS) counseling of the responsible physician.
Methods: Participants were 155 consecutive adult inpatients with SSTI and good quality clinical samples submitted to the microbiology laboratory from April 2016 to January 2017. Results of the rapid test and AMS recommendations were phoned through to the responsible physician. The comparison group was a historical cohort.
Results: Most SSTI were surgical wound infections (41.3% vs 38.1% for the intervention and comparison groups respectively) followed by diabetic foot (14.2% and 18.1%), abscesses (13.5% both) and cellulitis (12.9% both). Isolated microorganisms were mostly Gram-negative bacilli (two-thirds), followed by *Staphylococcus aureus* (SA). The ratio methicillin-susceptible SA (MSSA) to methicillin-resistant SA (MRSA) was 4:1. Improvements in the intervention cohort were: DOT (22.0 vs. 24.3 days, $p = 0.007$), treatment duration per SSTI episode (14.1 vs. 15.0 days, $p = 0.072$), treatment cost (433.1 vs. 533.3 €, $p = 0.039$), length of stay (18.6 vs 20.7 days, $p = 0.031$), related mortality (1 vs. 4 patients, $p = 0.022$) and *Clostridium*

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difficile infection (CDI) (4 vs. 8 patients, p = 0.050). In 48 cases (31.4%) in the intervention group, advice was given to improve empiric antibiotic treatment.
Conclusion: This type of program could help adjust antibiotic treatment when inappropriate, reducing antibiotic use and costs, length of stay, CDI and related mortality.

Introduction

Skin and soft tissue infections (SSTI) are common infections with a broad spectrum of presentations and etiologies.[1,2] In hospitalized patients the prevalence of SSTI has been estimated at 7%—10% and SSTI are common in an emergency care setting.[3] In both hospital-acquired and community-acquired SSTI, methicillin-resistant *Staphylococcus aureus* (MRSA) may be the responsible microorganism with clear implications for treatment, and social and economic impacts.[4]

Molecular tests can assess within a few hours the presence or absence of *S. aureus*.[5—9] In this prospective study, we assessed the clinical impacts of a fast track SSTI management program recently implemented at our hospital. This consists of running the GeneXpert® MSSA/MRSA SSTI test directly on good quality clinical samples from hospitalized patients with SSTI and communicating the results to the responsible physicians. Test results are provided with therapeutic advice within an antimicrobial stewardship (AMS) program.

Methods

Study design

This was a prospective study conducted at a teaching hospital (1550-bed) over the period April 2016—January 2017. We recruited 155 consecutive hospitalized adult patients with a clinical diagnosis of SSTI and a representative microbiologic sample submitted to the microbiology laboratory during working hours.

As a comparison group, a historical cohort of patients of the same institution, during the period January—December 2015, when the rapid molecular test GeneXpert® MSSA/MRSA SSTI was not available, was examined. Patients were matched for age, department, SSTI type and isolated microorganisms.

Sample processing

Our rapid diagnostic algorithm (Gram stain plus GeneXpert® MSSA/MRSA SSTI) was executed immediately upon sample arrival. This consists of first assessing the microbiological quality of the sample by assigning a Gram stained section a Q index according to the presence of polymorphonuclears[10,11]: samples showing a Q index $\geq$2 are classified as good quality. In the event that the sample submitted was considered to be invalid, it was rejected and the responsible physician was asked to send a new one. Next, the GeneXpert® MSSA/MRSA SSTI test is used on good quality samples following the manufacturer's instructions (Cepheid, Sunnyvale, CA) and other authors' recommendations for this type of sample.[12] Clinical samples are processed following standard procedures.[13,14]

Intervention

Microbiological results (positive or negative) were immediately reported by phone to the physician in charge. Data were collected on the infection and the antibiotic treatment. A clinical microbiology physician offered antibiotic treatment recommendations, following the IDSA and the Spanish Society of Chemotherapy guidelines for this type of infections.[2,15]

Data collection

Demographic, clinical, microbiological and treatment variables were collected. We recorded age, sex, admission service, Charlson index,[16] McCabe-Jackson index,[17] comorbidities, risk factors for MRSA infection, infection type and severity,[2] first episode or worsening infection (within the previous 90 days), and need for surgery. Information on antibiotic treatment included drug, dose, duration, and cost. The microbiological factors recorded were sample type, Gram staining, GeneXpert® result, culture result, and turn-around-time for the rapid algorithm and conventional culture. Information was also collected on *Clostridium difficile* infection (CDI), length of hospital stay (LOS), and related and unrelated mortality.

Regarding antibiotic treatment, a major recommendation was defined as that which led to the initiation or suspension of an antibiotic, and a minor recommendation as that which resulted in maintained, escalated or de-escalated antibiotic treatment.

Ethics committee on clinical research

The study protocol was approved and the need for informed consent was waived by the ethics committee of the Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Statistical analysis

Categoric variables appear with their frequency distributions. Continuous variables are provided as the mean and

standard deviation (SD), or median and interquartile range (IQR) if non-normally distributed. A propensity score-based sensitivity analysis, to compare outcomes among patients in both cohorts, was performed. A Poisson linear regression model was constructed for quantitative variables (DOT, DDD, days of therapy, antibiotic cost, LOS) and a logistic model for qualitative variables (need for surgery, CDI, related and unrelated mortality), through bootstrapping cluster analysis of pairs obtained in the design, matched for age (±7 years), department, SSTI type and microorganism, and adjusted for the variables in the cohorts that might introduce confusion (comorbidities, infection severity, first episode of SSTI, previous infection by *S. aureus)*. Relative effects are presented along with their 95% confidence intervals (incident rate ratio IRR for the Poisson model; odds ratio OR for the logistics model). Significance was set at $p < 0.05$.

Results

Characteristics of the cohorts

The characteristics of patients in both cohorts are provided in Table 1. Mean ages were 64.4 years (SD, 17.4) and 64.3 years (SD 17.2).

Comorbidities were found in 83.2% of patients; diabetes mellitus (39.4% and 44.5%) followed by heart disease (32.3% and 40.0%, respectively). The most common hospital departments were surgical (54.8% both groups) and medical (35.5% and 37.4%). Most SSTI were surgical wound infections (41.3% and 38.1%), followed by diabetic foot (14.2% and 18.1%), abscesses (13.5% both groups) and cellulitis (12.9% both groups). For most patients, the SSTI was a first episode (82.6% and 96.1%).

The risk factors for MRSA infection detected were mostly DM or a immunosuppressive disorder (51.0% and 58.1%), followed by broad-spectrum antibiotics in the preceding six months (31.6% % and 33.5%) and contact with the healthcare system or nursing home (23.2% and 21.3%). Very few patients had had a SSTI caused by MRSA in the previous year (3.9% and 1.3%).

Microbiology results

We received 155 samples with a Q score ≥2. The most common samples were wound exudates, followed by biopsies and abscesses (Table 1).

Positive cultures were obtained in 70.3% and 72.3% of the intervention and comparison patients, respectively, of which 46.8% and 40.2% respectively were monomicrobial (Table 2). The most commonly isolated microorganisms were Gram-negative bacilli, followed by *S. aureus*. Half the cultures in which MSSA was isolated were monomicrobial; for MRSA, this occurred in 4/11 patients.

Conventional culture versus GeneXpert® MRSA/SA SSTI

The performance of the GeneXpert® MRSA/SA SSTI assay was excellent for both MSSA and MRSA (accuracy 96.8%; 95% CI 93.7–99.9) (Table 3). There were no inhibitions or

Table 1 Characteristics of the intervention and comparison cohorts.

Variable	Intervention cohort (n = 155)	Comparison cohort (n = 155)
Age (years) (mean, SD[a])	64.4, 17.4	64.3, 17.2
Sex (n, %)		
Male	95 (61.3)	86 (55.5)
Female	60 (38.7)	69 (44.5)
Charlson index (mean, SD)	4.1 (3.0)	4.4 (3.2)
Department (n, %)		
Surgical	85 (54.8)	85 (54.8)
Medical	55 (35.5)	58 (37.4)
Intensive care	10 (6.5)	7 (4.5)
Immunosuppressed patients	5 (3.2)	5 (3.2)
McCabe index (n, %)		
Rapidly fatal	2 (1.3)	0 (0)
Ultimately fatal	24 (15.5)	22 (14.2)
Non-fatal	129 (83.2)	133 (85.8)
Infection severity (n, %)		
Mild	58 (37.4)	43 (27.7)
Moderate	85 (54.8)	103 (66.5)
Severe	12 (7.7)	9 (5.8)
Infection type (n, %)		
Surgical wound infection	64 (41.3)	59 (38.1)
Diabetic foot	22 (14.2)	28 (18.1)
Abscess	21 (13.5)	21 (13.5)
Cellulitis	20 (12.9)	20 (12.9)
Foliculitis	2 (1.3)	1 (0.6)
Erysipela	1 (0.6)	0 (0)
Ectima	1 (0.6)	0 (0)
Necrotizing fasciitis	1 (0.6)	0 (0)
Impetigo	0 (0)	1 (0.6)
Others (ulcers)	23 (14.8)	25 (16.1)
Comorbidities (n, %)		
Diabetes mellitus	61 (39.4)	69 (44.5)
Heart disease	50 (32.3)	62 (40.0)
Chronic renal failure	21 (13.5)	26 (16.8)
Solid tumor	19 (12.3)	25 (16.1)
Neurological disease	17 (11.0)	10 (6.5)
Chronic obstructive pulmonary disease	11 (7.1)	10 (6.5)
Liver disease	10 (6.5)	5 (3.2)
Psychiatric disease	10 (6.5)	11 (7.1)
Hematologic cancer	9 (5.8)	5 (3.2)
Solid organ transplant	4 (2.6)	3 (1.9)
Hemodialysis	3 (1.9)	2 (1.3)
Human immunodeficiency virus	2 (1.3)	1 (0.6)
No comorbidities	26 (16.8)	26 (16.8)
Risk factors for MRSA[b] (n, %)		
High risk patient (DM[c], IS[d])	79 (51.0)	90 (58.1)
Broad spectrum antibiotic treatment in previous 6 months	49 (31.6)	52 (33.5)
Previous hospitalization/ nursing home	36 (23.2)	33 (21.3)
Previous fluoroquinolones	7 (4.5)	3 (1.9)
Previous MRSA[b] infection	6 (3.9)	2 (1.3)
Prison inmate	4 (2.6)	1 (0.6)

Table 1 (*continued*)

Variable	Intervention cohort (n = 155)	Comparison cohort (n = 155)
Contact sport	1 (0.6)	0 (0)
Men who have sex with men	0 (0)	2 (1.3)
First SSTI[e] episode (n, %)		
Yes	128 (82.6)	149 (96.1)
No	27 (17.4)	6 (3.9)

[a]SD: standard deviation. [b]MRSA: methicillin-resistant *Staphylococcus aureus*. [c]DM: diabetes mellitus. [d]IS: immunosuppression. [e]SSTI: skin and soft tissue infection.

mechanical errors. In five samples, PCR and culture results did not match: there were two false negatives in a sample testing PCR-MRSA negative/culture-MRSA positive and a sample testing PCR-MSSA negative/culture-MSSA positive; and three false positives in samples testing PCR-MSSA positive and culture-MSSA negative. These patients were already on antimicrobial treatment. The median turn-around-time (TAT) until the first call to the clinician with rapid results and AMS advice was 4 h (IQR 3—5) compared to 99 h (IQR 53.75—124.0) for the comparison cohort (conventional culture).

Antibiotic treatment

In both cohorts, a high percentage of patients received antibiotic treatment (146/155 and 141/155) (Table 4). Over half of these patients received specific anti-staphylococcal drugs (84/146 or 57.5% and 73/141 or 51.8%), mainly with anti-MRSA activity. Antibiotics prescribed were vancomycin (in approximately one-third of cases), followed by clindamycin, co-trimoxazole, linezolid and daptomycin. The majority received a single antistaphylococcal antibiotic.

Communication of results and adjustment of empirical treatment

In 153/155 (98.7%) of the intervention patients, the results of the rapid test were communicated by telephone to the physician in charge; in 141/153 patients (92.2%) on the same day, and in 12/153 patients (7.8%) the next day. Only on two occasions was it not possible to speak to a doctor or nurse; both patients were receiving adequate empiric treatment. In 5/153 cases (3.3%) the patient was not receiving antibiotics, and the physician contacted considered them unnecessary (e.g., minor abscess treated with incision and drainage in an immunocompetent patient). Thus, the empiric management of SSTI was correct in 107 patients (102 receiving antibiotics and five not). In 48 patients (31.4%), it was deemed that empiric antibiotic treatment could be improved in terms of indication, drug, route, and dose, and advice was offered. Ten major and 88 minor recommendations were made. The advice given was taken in 32/48 (66.67%) cases: treatment against *S. aureus* was started or added in 17/32 patients (53.1%) (11 with a MSSA and 6 with a MRSA infection), while in 9 (28.1%) cases it was de-escalated or stopped.

Table 2 Microbiological results.

Variable (n, %)	Intervention cohort (n = 155) (n,%)	Comparison cohort (n = 155) (n,%)
Sample type		
Wound exudate	55 (35.5)	75 (48.4)
Surgical wound	34 (21.9)	29 (18.7)
Tissue biopsy	21 (13.6)	18 (11.6)
Abscess	19 (12.3)	15 (9.6)
Skin wound	12 (7.7)	10 (6.5)
Eschar	12 (7.7)	8 (5.2)
Percutaneous aspirate	2 (1.3)	0 (0)
Culture results		
Saprophytic flora	29/155 (18.7)	27/155 (17.4)
Sterile culture	17/155 (11.0)	16/155 (10.3)
Positive culture, total	109/155 (70.3)	112/155 (72.3)
Monomicrobial culture	51/109 (46.8)	45/112 (40.2)
Polymicrobial culture	58/109 (53.2)	67/112 (59.8)
TAT[a] (hours) (median, IQR)	4 (3—5)	99 (53.8—124.0)
Isolated pathogens		
MSSA[b]	42/109 (38.5)	42/112 (37.5)
MRSA[c]	11/109 (10.1)	11/112 (9.8)
Total *S. aureus* isolated	53/109 (48.6)	53/112 (47.3)
Streptococcus pyogenes	1/109 (0.9)	2/112 (1.8)
Enterobacteriaceae	72/109 (66.1)	69/112 (61.6)
Pseudomonas spp.	11/109 (10.1)	15/112 (13.4)
Other GNB	7/109 (6.4)	6/112 (5.4)
Other	78/109 (71.6)	85/112 (75.9)
Isolation of *S. aureus*		
Monomicrobial MSSA[b]	21 (19.3)	22 (19.6)
Polymicrobial MSSA[b]	21 (19.3)	20 (17.9)
Monomicrobial MRSA[c]	4 (3.7)	8 (7.1)
Polymicrobial MRSA[c]	7 (6.4)	3 (2.7)
Blood cultures taken	29 (18.7)	22 (14.2)
Positive	7/29 (21.4)	4/22 (18.2)

[a]TAT: turn-around time. [b]MSSA: methicillin susceptible *Staphylococcus aureus*. [c]MRSA: methicillin-resistant *Staphylococcus aureus*.

In five patients, the results of the rapid algorithm (Gram-negative bacilli in Gram stain and a negative GeneXpert® result for *S. aureus*) allowed for treatment against Gram-negative bacilli only to be initiated.

Although in most of the cases no Gram-negative bacilli were visible in the Gram stain, discontinuation of the empiric antibiotic treatment against these microorganisms was not recommended, as our rapid diagnostic algorithm was not intended for the detection of these microorganisms.

In sixteen patients (33.3%), the responsible physicians decided not to follow the advice. Reasons were: they preferred to wait for culture results (7 cases, 43.7%); they did not want any advice (6 cases, 37.5%); treatment modification was not possible (1 case, 6.3%); and the

Table 3 Performance of the Xpert™ MRSA/SA SSTI test used on 155 clinical SSTI samples.

Microorganism	Prevalence	Sensitivity	Specificity	PPV[a]	NPV[b]	PLR[c]	NLR[d]	Accuracy
MSSA[e]	27.3 (19.9–34.6)	97.6 (91.8–100.0)	97.3 (93.9–100.0)	93.2 (84.6–100.0)	99.1 (96.9–100.0)	36.4 (11.9–111.4)	0.02 (0.00–0.17)	97.4 (94.6–100.0)
MRSA[f]	7.1 (2.8–11.5)	90.9 (69.4–100.0)	100.0 (99.7–100.0)	100.0 (95.0–100.0)	99.3 (97.6–100.0)	–	0.09 (0.01–0.59)	99.4 (97.8–100.0)

Data are presented in percentage and 95% CI. [a]PPV: positive predictive value. [b]NPV: negative predictive value. [c]PLR: positive likelihood ratio (for MRSA, there were no false positive results). [d]NLR: negative likelihood ratio. [e]MSSA: methicillin-susceptible *Staphylococcus aureus*. [f]MRSA: methicillin-resistant *S. aureus*.

physician could not be contacted (2 cases, 12.5%). When we compared these two groups in the intervention cohort, patients whose physicians followed the advice provided showed relative reductions in antibiotic costs of 69.1% (160.9 vs. 521.2 €, p = 0.023) and in DOT of 40% (15 vs. 25 days, p = 0.039).

Clinical impacts of the rapid diagnostic algorithm

The bootstrap cluster analysis was matched for age, department, infection type (superficial, medium, deep), microorganism, and adjusted for diabetes mellitus, neurological disease, first episode of SSTI, infection severity and previous MRSA infection. This statistical analysis revealed relative reductions in the intervention group of 9.3% in DOT (22.0 vs. 24.3 days, p = 0.007), 5.5% in treatment duration per SSTI episode (14.1 vs. 15.0, p = 0.072), 21.7% in antibiotic costs (433.1 vs. 533.3 €, p = 0.039) and 10.2% in LOS (18.6 vs 20.7 days, p = 0.031 (Table 5). We also detected relative reductions of 75.5% in related mortality (1 vs. 4 patients, p = 0.022) and 51.3% in CDI (4 vs. 8 patients, p = 0.050). No significant differences emerged between the cohorts in DDD (25.6 vs. 27.6, p = 0.454), unrelated mortality (6 vs. 8 patients, p = 0.595) and need for SSTI surgery (63 vs. 50 patients, p = 0.107).

Discussion

The results of our study indicate that a rapid diagnostic algorithm for SSTI followed by immediate communication of results and advice to the responsible physician leads to reduced antibiotic use, hospital expenses, length of stay, CDI and related mortality. This algorithm consists of Gram staining of clinical samples to pre-select a good quality sample and the molecular detection of *S. aureus* directly on the sample (GeneXpert® MRSA/SA SSTI) accompanied by AMS. SSTI are a common cause of infections in hospitalized patients, generating high morbidity and mortality and increased costs.[18–20] Gram-positive microorganisms, particularly *S. aureus*, are a common cause of SSTI[1,21–24] and the participation of MRSA strains is increasingly being reported in the range 1% to over 80% with vast regional variations.[4,25–27] As clinical and epidemiologic factors alone do not adequately predict the likelihood of MRSA infection, most guidelines recommend empiric treatment covering MRSA.[2]

Culture-directed antimicrobial therapy in which MRSA is confirmed or ruled out is often delayed for more than 48 h, with consequences for morbidity and mortality.[1,28,29]

PCR tests such as the one used here are starting to show their potential for AMS improvement. The GeneXpert® MRSA/SA SSTI assay has received FDA approval for the diagnosis of SSTI directly on clinical samples and has been validated in different studies.[12,30] In our study, the accuracy of this molecular test was 97.4% for MSSA and 99.4% for MRSA.

Using the PCR test directly on good quality clinical samples, we found good correlation with culture based results. In both our cohorts (intervention and comparison), *S. aureus* was culture detected in 53 patients (48.6%). The PCR test was able to anticipate the identity and betalactam susceptibility of the bacterium in 51/53 of cases (96.2%).

Table 4 Antibiotics administered (number of patients).

	Intervention cohort		Comparison cohort		p value
	n	%	n	%	
Antibiotics against MSSA[a] (cloxacillin)	13/146	8.9	4/141	2.8	0.054
Antibiotics against MRSA[b]	71/146	48.6	69/141	48.9	0.947
VAN	23/71	32.4	34/69	49.3	0.063
DAP	12/71	16.9	16/69	23.2	0.473
LZD	13/71	18.3	21/69	30.4	0.140
CLI	23/71	32.4	15/69	21.7	0.219
SXT	15/71	21.1	15/69	21.7	0.906
Monotherapy against MRSA	57/71	80.3	50/69	72.5	0.373
Combination therapy against MRSA	14/71	19.7	19/69	27.5	0.373
Antibiotics against GNB					
PEN plus inhibitor	84/146	57.5	87/141	61.7	0.549
Cephalosporins	34/146	23.3	25/141	17.7	0.308
CAZ	2/146	1.4	3/141	2.1	0.968
Fluoroquinolone	40/146	27.4	37/141	26.2	0.930
Carbapenems	42/146	28.8	43/141	30.5	0.848

[a]MSSA: methicillin-susceptible *Staphylococcus aureus*. [b]MRSA: methicillin-resistant *Staphylococcus aureus*.

Three false positive results (1.9%) were produced in patients already on antimicrobial therapy. False negative results were observed in two cases (1.3%). We speculate that this was due to a very low bacterial count in the samples, under the test's limit of detection. This assay allows for the quick adjustment of empiric antibiotic treatment without having to wait for definitive microbiological results. The median times in our intervention and comparison groups until a positive result was obtained from the microbiology department were 4 h versus 99 h, respectively.

Significant differences in favor of the intervention cohort were observed in the following variables: DOT (22.0 vs. 24.3 days, $p = 0.007$), antibiotic treatment duration per SSTI episode (14.1 vs. 15.0 days, $p = 0.072$), antibiotic costs (433.1 vs. 533.3 €, $p = 0.039$) and LOS (18.6 vs. 20.7 days, $p = 0.031$). In addition, we also noted relative reductions of 75.5% in related mortality (1 vs. 4 patients, $p = 0.022$) and of 51.3% in CDI (4 vs. 8 patients, $p = 0.050$). To the best of our knowledge, this is the first study to detect a reduction in mortality in response to a similar intervention in this patient setting.

There are studies that show that appropriate empiric antibiotic treatment reduces mortality in severe sepsis and septic shock, from the first hour.[31] This has also been found

Table 5 Regression models of relative effects of the variables examined.

Variable	Intervention cohort	Comparison cohort	IRR[a]/OR[b] (95% CI)	p value
DDD[c] (mean, SD[d])	25.6 (26.3)	27.6 (31.5)	0.929 (0.77—1.13)	0.454
DOT[e] (days) (mean, SD[d])	22.0 (21.5)	24.3 (24.1)	0.907 (0.84—0.97)	0.007
Length of treatment (days) (mean, SD[d])	14.1 (12.8)	15.0 (13.7)	0.945 (0.89—1.00)	0.072
Cost (€) (mean, SD[d])	433.1 (678.8)	533.3 (909.3)	0.783 (0.62—0.99)	0.039
LOS[e] (days) (mean, SD[d])	18.6 (20.9)	20.7 (25.1)	0.898 (0.81—0.99)	0.031
Need for surgery (n, %)	63.0 (40.6)	50.0 (32.3)	1.438 (0.96—2.24)	0.107
CDI[f] (n, %)	4.0 (2.6)	8.0 (5.2)	0.487 (0.24—1.00)	0.050
Related mortality (n, %)	1.0 (0.6)	4.0 (2.6)	0.245 (0.07—0.81)	0.022
Unrelated mortality (n, %)	6.0 (3.9)	8.0 (5.2)	0.740 (0.24—2.25)	0.595

[a]IRR, incident rate ratio; [b]OR, odds ratio; [c]CI, confidence interval; [d]DDD, defined daily dose; [e]SD, standard deviation; [f]DOT, days of therapy; [g]LOS: length of stay. [h]CDI: *Clostridium difficile* infection.
Bootstrap clustered analysis matched for age, department, infection type (superficial, medium, deep), and microorganism.
Models adjusted for comorbidities (diabetes mellitus, neurological disease), first SSTI episode, prior MRSA infection) and infection severity.

for other infections, like pneumonia. In our case, the fast microbiological diagnosis allowed the start of an adequate antibiotic treatment, which was earlier in the intervention cohort. We might speculate that this is what led to a lower mortality in our study. Studies assessing the use of this assay accompanied by therapeutic advice have generated different results. One such study failed to show improved patient outcomes or reduced antibiotic use in patients with SSTI caused by *S. aureus*.[32] The practice bundle introduced by these authors consisted of the use of this assay for inpatients admitted from the emergency department with physician education and pharmacist guidance. However, despite the test's accuracy, the authors were unable to reduce unnecessary empiric anti-MRSA antibiotics and concluded that introducing a rapid diagnostic test in the absence of an effective implementation strategy is insufficient to produce the expected results. In another study, the use of the assay in patients with cutaneous abscesses in the emergency department allowed for more targeted antibiotic selection but without impacts on clinical outcomes. Regretfully, many patients were not prepared to wait for the molecular test results, prompting the empiric administration of antibiotics.[33]

The key to successful rapid diagnostic testing is the communication of results to an AMS team. This means that the team can notify clinicians of test results and guide their decision to initiate or modify antimicrobial therapy. Without this link between clinical microbiologists and AMS, we risk losing any rapid microbiologic results.[9,34,35]

Our recently introduced fast track program is implemented by expert clinical microbiologists to allow for good assessment of the antibiotic treatment the patient is receiving and its adjustment based on rapid microbiological results.

The main limitation of our study is that it was not randomized. Otherwise, it is robust and methodologically sound. Both cohorts were carefully matched for age, department, SSTI type and isolated microorganisms. Both cohorts were from the same hospital. The antibiotic policy did not change in the hospital between both periods of time. Briefly, there were no changes in patient management. Even more, the models constructed were adjusted for comorbidities showing small differences between them that could act as confounding factors.

A further limitation is that we did not address the potential effects of time to antibiotic administration on patient outcomes. Besides, samples were processed only during regular working hours.

Our findings support the continued use and monitoring of our fast track algorithm for hospitalized patients with SSTI and highlight the key role played by rapid AMS advice to clinicians.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Garau J, Ostermann H, Medina J, Avila M, McBride K, Blasi F, et al. Current management of patients hospitalized with complicated skin and soft tissue infections across Europe (2010-2011): assessment of clinical practice patterns and real-life effectiveness of antibiotics from the REACH study. *Clin Microbiol Infect* 2013;**19**:E377—85.
2. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis* 2014;**59**:147—59.
3. Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *Can J Infect Dis Med Microbiol* 2008;**19**:173—84.
4. Nathwani D, Eckmann C, Lawson W, Solem CT, Corman S, Stephens JM, et al. Influence of real-world characteristics on outcomes for patients with methicillin-resistant Staphylococcal skin and soft tissue infections: a multi-country medical chart review in Europe. *BMC Infect Dis* 2014;**14**:476.
5. Nathwani D. Impact of methicillin-resistant *Staphylococcus aureus* infections on key health economic outcomes: does reducing the length of hospital stay matter? *J Antimicrob Chemother* 2003;**51**(Suppl 2):ii37—44.
6. Lipsky BA, Napolitano LM, Moran GJ, Vo L, Nicholson S, Chen S, et al. Economic outcomes of inappropriate initial antibiotic treatment for complicated skin and soft tissue infections: a multicenter prospective observational study. *Diagn Microbiol Infect Dis* 2014;**79**:266—72.
7. Ostermann H, Blasi F, Medina J, Pascual E, McBride K, Garau J. Resource use in patients hospitalized with complicated skin and soft tissue infections in Europe and analysis of vulnerable groups: the REACH study. *J Med Econ* 2014;**17**:719—29.
8. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. *Clin Infect Dis* 2016;**62**:e51—77.
9. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. *Clin Infect Dis* 2014;**59**(Suppl 3):S134—45.
10. Sharp SE, Robinson A, Saubolle M, Santa Cruz M, Carroll K, Baselski V. *Cumitech 7B, lower respiratory tract infections*. Washington, DC: ASM Press; 2004.
11. Matkoski C, Sharp SE, Kiska DL. Evaluation of the Q score and Q234 systems for cost-effective and clinically relevant interpretation of wound cultures. *J Clin Microbiol* 2006;**44**:1869—72.
12. Dubouix-Bourandy A, de Ladoucette A, Pietri V, Mehdi N, Benzaquen D, Guinand R, et al. Direct detection of *Staphylococcus* osteoarticular infections by use of Xpert MRSA/SA SSTI real-time PCR. *J Clin Microbiol* 2011;**49**:4225—30.
13. Chan WW. Gram stain. In: Leber AL, editor. *Clinical microbiology procedures handbook*. 4th ed. Washington, DC: ASM; 2016. p. 3.2.1.-3.2.1.21.
14. Carson JA. Wound cultures. In: Leber AL, editor. *Clinical microbiology procedures handbook*. 4th ed. Washington, DC: ASM; 2016. p. 3.13.1.1.-3.13.2.4.
15. Sociedad Espanola de Quimioterapia, Sociedad Espanola de Medicina Interna, Asociacion Espanola de Cirujanos. Treatment guide for skin and soft tissue infections. Spanish Chemotherapy

society, Spanish internal medicine society, Spanish association of surgeons. *Rev Española Quimioter* 2006;**19**:378—94.
16. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;**47**: 1245—51.
17. McCabe WR, Jackson GG. Gram-negative bacteremia. I. Etiology and ecology. *Arch Intern Med* 1962;**110**:847—64.
18. Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznik A, Oster G. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. *Infect Control Hosp Epidemiol* 2008;**29**:160—9.
19. Loo LW, Liew YX, Lee W, Chlebicki P, Kwa AL. Impact of antimicrobial stewardship program (ASP) on outcomes in patients with acute bacterial skin and skin structure infections (ABSSSIs) in an acute-tertiary care hospital. *Infect Dis Ther* 2015;**4**:15—25.
20. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis* 2016;**29**: 109—15.
21. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ. Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. *Clin Infect Dis* 2010;**51**:895—903.
22. Tognetti L, Martinelli C, Berti S, Hercogova J, Lotti T, Leoncini F, et al. Bacterial skin and soft tissue infections: review of the epidemiology, microbiology, aetiopathogenesis and treatment: a collaboration between dermatologists and infectivologists. *J Eur Acad Dermatol Venereol* 2012;**26**:931—41.
23. Ray GT, Suaya JA, Baxter R. Microbiology of skin and soft tissue infections in the age of community-acquired methicillin-resistant *Staphylococcus aureus*. *Diagn Microbiol Infect Dis* 2013; **76**:24—30.
24. Garau J, Blasi F, Medina J, McBride K, Ostermann H, Rs group. Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. *BMC Infect Dis* 2015;**15**:78.
25. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. *BMC Infect Dis* 2013;**13**:252.
26. Dukic VM, Lauderdale DS, Wilder J, Daum RS, David MZ. Epidemics of community-associated methicillin-resistant *Staphylococcus aureus* in the United States: a meta-analysis. *PLoS One* 2013;**8**:e52722.
27. Jones RN, Flonta M, Gurler N, Cepparulo M, Mendes RE, Castanheira M. Resistance surveillance program report for selected European nations (2011). *Diagn Microbiol Infect Dis* 2014;**78**:429—36.
28. Nathwani D, Eckmann C, Lawson W, Stephens JM, Macahilig C, Solem CT, et al. Pan-European early switch/early discharge opportunities exist for hospitalized patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections. *Clin Microbiol Infect* 2014;**20**:993—1000.
29. Marwick C, Broomhall J, McCowan C, Phillips G, Gonzalez-McQuire S, Akhras K, et al. Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. *J Antimicrob Chemother* 2011;**66**: 387—97.
30. Wolk DM, Struelens MJ, Pancholi P, Davis T, Della-Latta P, Fuller D, et al. Rapid detection of *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) in wound specimens and blood cultures: multicenter preclinical evaluation of the Cepheid Xpert MRSA/SA skin and soft tissue and blood culture assays. *J Clin Microbiol* 2009;**47**:823—6.
31. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014;**42**:1749—55.
32. Terp S, Krishnadasan A, Bowen W, Joo J, Furoy D, Chan J, et al. Introduction of rapid methicillin-resistant *Staphylococcus aureus* polymerase chain reaction testing and antibiotic selection among hospitalized patients with purulent skin infections. *Clin Infect Dis* 2014;**58**:e129—32.
33. May LS, Rothman RE, Miller LG, Brooks G, Zocchi M, Zatorski C, et al. A randomized clinical trial comparing use of rapid molecular testing for *Staphylococcus aureus* for patients with cutaneous abscesses in the emergency department with standard of care. *Infect Control Hosp Epidemiol* 2015;**36**:1423—30.
34. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the microbiology laboratory can right the ship. *Clin Microbiol Rev* 2017;**30**:381—407.
35. Buehler SS, Madison B, Snyder SR, Derzon JH, Cornish NE, Saubolle MA, et al. Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a laboratory medicine best practices systematic review and meta-analysis. *Clin Microbiol Rev* 2016; **29**:59—103.