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Microbiology of acute bacterial skin and skin-structure infections in Greece: A proposed clinical prediction score for the causative pathogen

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ABSTRACT

Although clinical definitions of acute bacterial skin and skin-structure infection (ABSSSI) are now well established, guidance of the prediction of likely pathogens based on evidence is missing. This was a large survey of the microbiology of ABSSSIs in Greece. During the period November 2014 to December 2016, all admissions for ABSSSI in 16 departments of internal medicine or surgery in Greece were screened to determine the likely bacterial aetiology. Samples were cultured on conventional media. Expression of the *SA442*, *mecA*/*mecC* and *SCCmec-orfX junction* genes was assessed. Following univariate and forward logistic regression analysis, clinical characteristics were used to develop scores to predict the likely pathogen with a target of 90% specificity. In total, 1027 patients were screened and 633 had positive microbiology. Monomicrobial infection by Gram-positive cocci occurred in 52.1% and by Gram-negative bacteria in 20.5%, and mixed infection by Gram-positive cocci and Gram-negative bacteria in 27.3%. The most common isolated pathogens were *Staphylococcus aureus* and coagulase-negative staphylococci. Resistance to methicillin was 57.3% (53.5–61.1%). Three predictive scores were developed: one for infection by

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methicillin-resistant *S. aureus*, incorporating recent hospitalisation, atrial fibrillation, residency in long-term care facility (LTCF) and stroke; one for mixed Gram-positive and Gram-negative infections, incorporating localisation of ABSSSI in lumbar area, fluoroquinolone intake in last 6 days, residency in LTCF and stroke; and another for Gram-negative infection, incorporating skin ulcer presentation, peptic ulcer and solid tumour malignancy. In conclusion, methicillin-resistant staphylococci are the main pathogens of ABSSSIs. The scores developed may help to predict the likely pathogen.

1. Introduction

The increasing prevalence of skin and soft-tissue infections (SSTIs) poses a considerable healthcare burden in Europe, accompanied by significant morbidity. Acute bacterial skin and skin-structure infections (ABSSSIs) are among the most common reasons for hospitalisation with infection, prompting for the need for strategies to prevent and manage infection. In Europe, according to the European Centre for Disease Prevention and Control (ECDC), ABSSSIs represent 4% of all healthcare-associated infections [1]. The main pathogen isolated is *Staphylococcus aureus* [2].

Isolation rates of methicillin-resistant *S. aureus* (MRSA) vary significantly among European countries, ranging between 0.9% in the Netherlands to 56.0% in Romania [3]. In the USA, there has been a major reported increase in MRSA infections in the past 20 years, which is directly associated with the parallel increase in the incidence of purulent SSTIs [4]. However, recent data from the US Centers for Disease Control and Prevention (CDC) suggest that the estimated overall incidence has significantly decreased since 2005 [5], which is in line with the decrease observed in Europe (18.6% in 2011 versus 17.4% in 2014) [3].

A definition of ABSSSI has recently been introduced by the US Food and Drug Administration (FDA) [6]. However, available epidemiology and resistance trends following the introduction of the ABSSSI definition are not yet available. In Greece, the AIDA randomised clinical trial was performed during the period November 2014 to December 2016. Although only patients infected by MRSA could participate in the AIDA trial, in order to screen for these patients, a large-scale microbiological survey was conducted among all patients with ABSSSI. The results of this extensive screening process are analysed here, aiming to identify clinical signs that can provide guidance on the likely type of pathogen. The resistance rates of the isolated pathogens were also analysed.

2. Patients and methods

2.1. Study design

The current analysis uses the results from screening for the microbiological evaluation of patients admitted with skin infections in 16 departments of internal medicine or surgery in Greece who participated in the AIDA trial. AIDA is a prospective, open-label, randomised controlled clinical trial, with pharmacokinetic/pharmacodynamic validation, to compare antimicrobial treatment with oral minocycline plus rifampicin to treatment with oral linezolid for ABSSSIs caused by MRSA (EudraCT no. 2014-001276-56). The study protocol was approved by the Ethics Committees of the hospitals of the participating study sites, by the National Ethics Committee of Greece and by the National Organization for Medicines of Greece. Patients were enrolled after written informed consent was provided by themselves or by their first-degree relatives in the case of patients unable to consent.

Inclusion criteria were: (i) age $\geq$18 years; (ii) either sex; (iii) ulcer, first- or second-degree burn of $<$20% of the body surface area with concomitant signs of cellulitis, major abscess, deep or extensive cellulitis, wound, trauma or post-surgical infection; (iv) local inflammation with $\geq$75 cm^2 dimension; (v) purulent or seropurulent drainage; (vi) at least two among erythema extending by $\geq$1 cm from the lesion edge, swelling and/or induration, warmth, pain and/or tenderness at palpation; and (vii) at least one of core temperature $>$38 °C, total white blood cell (WBC) count $>$10 000/mm^3 and immature neutrophil band $>$15% regardless of the total WBC count.

The main exclusion criteria were diabetic foot infection, confirmed osteomyelitis, severe hepatic function impairment, end-stage renal disease, and administration of antimicrobials for the episode of ABSSSI making them eligible for the study in the last 24 h. Recent administration of antimicrobials for other infections was not an exclusion criterion.

Patients hospitalised with ABSSSI between 1 November 2014 and 31 December 2016 were enrolled. Recorded information included demographics, type of infection, days of hospitalisation (if any) before development of ABSSSI, type and administered antibiotics in the last 3 months, and medical history.

2.2. Laboratory investigation

Two samples of draining pus were collected from each patient using a sterile cotton swab. Sampling was done after cleaning the skin surface with an alcoholic solution and by inserting the swab deeply towards the source of draining pus using the Levine technique. The first swab was placed in transfer gel and was used for microbiological culture. The second swab was used for real-time PCR for the detection of *S. aureus*. Samples from all patients were transferred to the central laboratory located at the 4th Department of Internal Medicine of ATTIKON University General Hospital (Athens, Greece). Qualitative cultures were performed by plating the pus on CHROMagar™ selective for MRSA (Bioprepare, Attiki, Greece), on MacConkey agar (Beckton Dickinson, Sparks, MD, USA) and on mannitol salt agar (MSA) (Oxoid Ltd., Basingstoke, UK). Plates were incubated under aerobic conditions for 18–24 h at 37 °C. Following incubation, MRSA colonies on the CHROMagar™ dish had a pink colour. The presence of yellow colonies on MSA indicated the presence of *S. aureus*, which was confirmed by positive catalase and coagulase tests (Remel Inc., Lenexa, KS, USA). Colonies grown on MacConkey agar were identified using a BD BBL™ Crystal™ Bacterial Identification System (Beckton Dickinson). Susceptibilities of Gram-negative bacteria were determined by the disk diffusion method applying antimicrobial disks (Oxoid Ltd.) of 30 μg of amoxicillin/clavulanic acid, 5 μg of tigecycline, 30 μg of cefotaxime and 5 μg of moxifloxacin. Susceptibility testing with 30 μg of cefoxitin (Oxoid Ltd.) was performed by the Kirby–Bauer method for all staphylococcal isolates. All results were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints v.8.0 (http://www.eucast.org/clinical_breakpoints/). Multiplex PCR was performed using a RIDA®GENE MRSA detection kit (R-Biopharm AG, Darmstadt, Germany) detecting the presence of the *SA442*, *mecA*/*mecC* and *SCCmec-orfX junction* genes. The test allowed

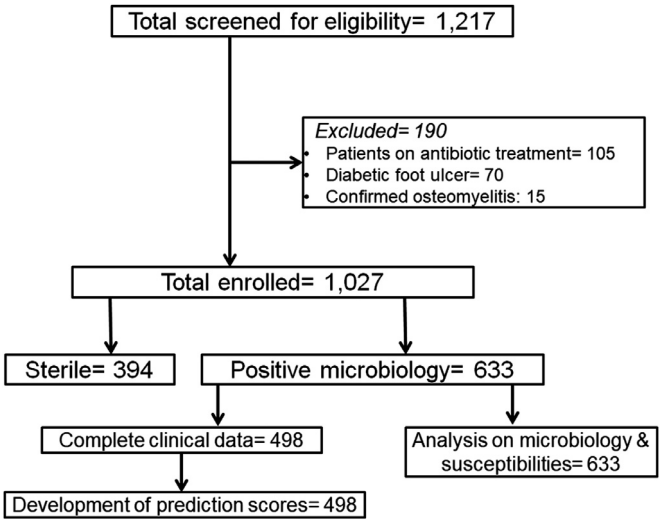

Fig. 1. Study flow chart.

the detection of MRSA, methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant coagulase-negative *Staphylococcus* spp. (MRCNS). Patients with at least one conventional or molecular test positive for either MRSA, MSSA or MRCNS were considered infected by the respective species.

2.3. Study endpoints

The primary endpoint was identification of likely pathogens associated with ABSSSIs. Secondary endpoints were (i) the resistance profile of isolated pathogens and (ii) the development of clinical variables guiding the prediction of the causative pathogen.

2.4. Statistical analysis

Results were provided as frequency and confidence interval (CI) and were compared by the Fisher's exact test. In order to develop clinical scores for prediction of the likelihood of infection by certain bacterial species, characteristics of patients infected and non-infected by that species were compared and those differing significantly were entered into forward logistic regression analysis. The *b* slopes of the analysis for significant variables were used to develop scores. Scores were further analysed by the design of receiver operator characteristic curves, and the co-ordinate points of the curves providing specificity >90% were depicted. The odds ratio and 95% CI of the cut-offs for a specific pathogen were determined according to the Mantel–Haenszel test. A *P*-value of <0.05 was considered statistically significant.

3. Results

The study flow chart is shown in Fig. 1. The primary study endpoint and the first secondary endpoint of susceptibility trends were available for 633 patients. Full clinical data were available for 498 of the 633 patients and this group was used for the second secondary endpoint analysis to predict likely pathogens.

Monomicrobial infection by Gram-positive cocci occurred in 52.1% of patients and by Gram-negative bacteria in 20.5% of patients, and mixed bacterial infections by both Gram-positive cocci and Gram-negative bacteria in 27.3% of patients (Fig. 2A). The most common isolated pathogens were MRCNS and MRSA, followed by MSSA (Fig. 2B).

Table 1
Forward logistic regression analysis of variables associated with the implicated pathogen of acute bacterial skin and skin-structure infection (ABSSSI).

Variable	OR (95% CI)	*P*-value
Methicillin-resistant *Staphylococcus aureus* (MRSA)		
Female sex	0.67 (0.44–1.02)	0.060
Atrial fibrillation	0.46 (0.26–0.82)	0.008
Hospitalisation in last 90 days	1.61 (1.05–2.46)	0.029
Residency in LTCF	3.48 (1.43–8.44)	0.006
Ischaemic stroke	1.89 (1.15–3.09)	0.012
Methicillin-resistant *Staphylococcus* spp.		
ABSSSI of lower extremity	0.60 (0.33–1.09)	0.093
ABSSI of lumbar area	1.65 (0.95–2.88)	0.073
Recent intake of clindamycin	3.36 (1.62–6.97)	0.001
COPD	2.70 (1.43–5.11)	0.002
Mixed Gram-positive/Gram-negative		
Cellulitis	0.00 (0.00–nc)	0.998
Abscess	0.17 (0.02–1.34)	0.093
Wound	0.49 (0.14–1.69)	0.259
Infection of lower extremity	1.08 (0.57–2.04)	0.795
Infection of lumbar area	2.02 (1.10–3.70)	0.023
Recent intake of fluoroquinolones	0.19 (0.06–0.67)	0.009
Residency in LTCF	2.47 (1.02–6.00)	0.045
Ischaemic stroke	1.79 (1.06–2.03)	0.031
Gram-negative bacteria		
Ulcer	2.87 (1.11–7.39)	0.029
Infection of lumbar area	1.25 (0.65–2.41)	0.508
Recent intake of carbapenems	2.42 (0.80–7.25)	0.116
Recent intake of glycopeptides	1.09 (0.64–6.88)	0.223
Dementia	1.76 (0.87–3.53)	0.106
Peptic ulcer	3.90 (1.18–12.94)	0.026
Solid tumour malignancy	2.43 (1.16–5.09)	0.019

OR, odds ratio; CI, confidence interval; LTCF, long-term care facility; COPD, chronic obstructive pulmonary disease; nc, not calculated.

Regarding infections where only Gram-positive pathogens were isolated, the most common pathogen was MSSA, followed by MRSA (Supplementary Fig. S1A). Among patients infected only by Gram-negative bacteria, the most common pathogen was *Klebsiella pneumoniae*, followed by *Pseudomonas aeruginosa* (Supplementary Fig. S1B). Among patients infected by both Gram-positive cocci and Gram-negative bacteria, the most common isolated pathogens were MRCNS, followed by *K. pneumoniae* and MRSA (Supplementary Fig. S1C). The frequencies of MRSA and MSSA isolation by the techniques used are provided in Supplementary Fig. 2.

The overall level of resistance to methicillin among the 633 patients with positive microbiology was 57.3% (53.5–61.1%). High resistance rates were also found for the Gram-negative pathogens (Fig. 3).

We next tried to develop a scoring system that can provide, with specificity >90%, the likelihood of infection by MRSA, MRCNS, mixed infections by both Gram-positive cocci and Gram-negative bacteria, and only Gram-negative bacteria. In order to achieve this, clinical characteristics of patients infected or non-infected by these pathogens were compared (Supplementary Tables S1–S4) and variables that differed significantly were entered into forward logistic regression analysis (Table 1). Based on the results, three scores were developed (Fig. 4). The score for MRSA took into consideration medical history of hospitalisation in the last 90 days, atrial fibrillation, ischaemic stroke and residency in a long-term care facility (LTCF), providing a specificity of 93.2% (90.2–95.4%). The score for infections by both Gram-positive cocci and Gram-negative bacteria took into consideration location of ABSSSI in the lumbar area, fluoroquinolone intake in the last 6 days, ischaemic stroke and residency in a LTCF, providing a specificity of 91.4% (88.2–93.8%). The score for infection only by Gram-negative bacteria took into consideration ABSSSI appearing as an ulcer, medical history of peptic ulcer and solid tumour malignancy, providing a specificity of 98.2% (96.5–99.1%). It was not possible to develop a similar score

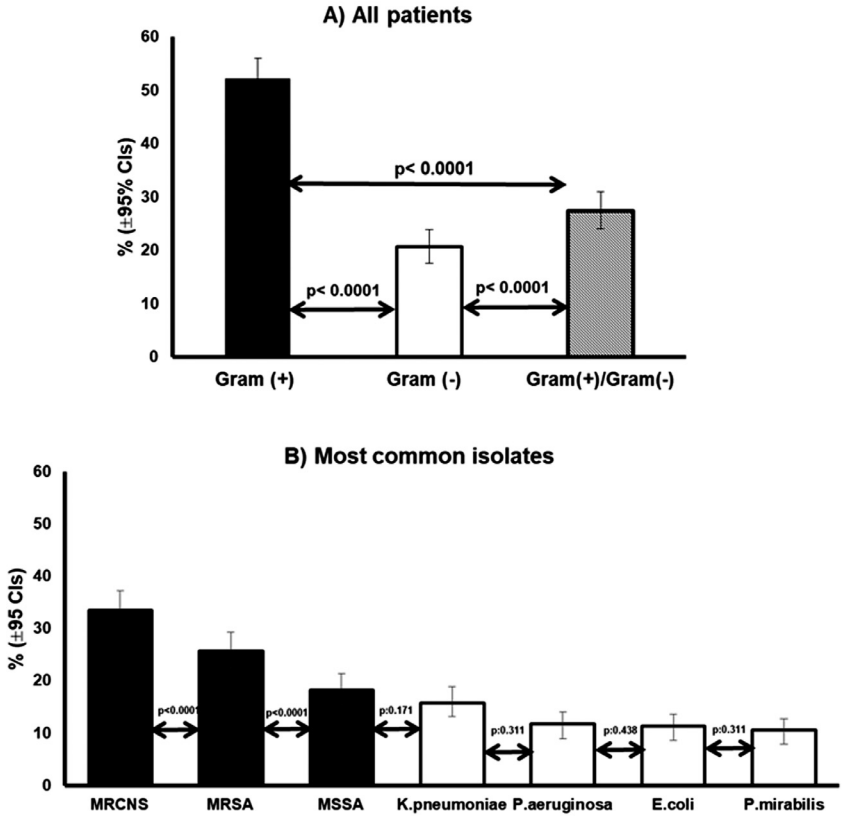

Fig. 2. Pathogen distribution among patients with positive microbiology for acute bacterial skin and skin-structure infection: (A) distribution into monomicrobial Gram-positive infection, monomicrobial Gram-negative infection, or mixed Gram-positive and Gram-negative infections; and (B) most common pathogens. *P*-values refer to indicated comparisons. CI, confidence interval; MRCNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

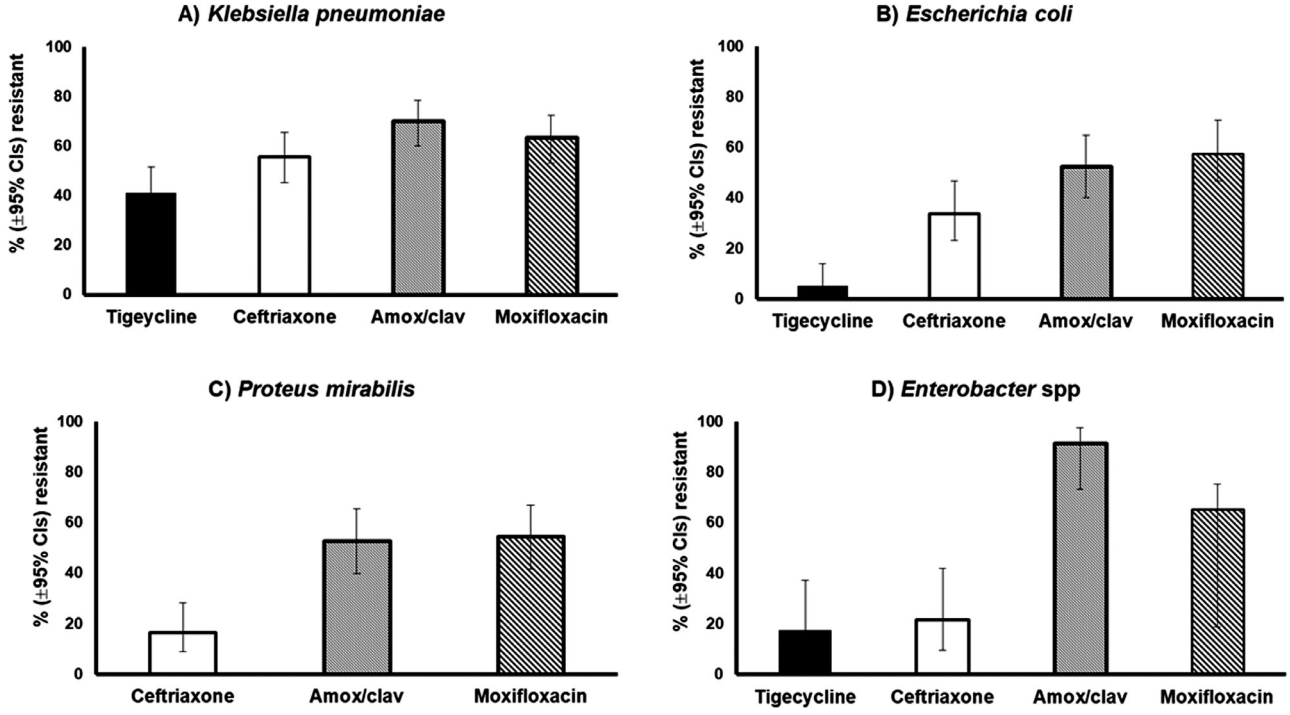

Fig. 3. Resistance rates of isolated Gram-negative pathogens. CI, confidence interval. Amox/clav, amoxicillin/clavulanic acid.

A)

Score for MRSA=
Hospitalization <90 days x 5 - atrial fibrillation x 4
+ residency in LTCF x 12 + ischaemic stroke x 6

	MRSA (n)	Non-MRSA (n)	
Score ≥12	24 Sens= 16.8% PPV= 50.0%	24	48
Score <12	118	332 Spec= 93.2% NPV= 73.8%	450
	142	356	498

OR= 2.74 (95% CIs= 1.48-5.06); p: 0.001

B)

Score for Gram(+)/Gram(-)=
Infection of the lumbar area x 7 - quinolone intake x 16
+ residency in LTCF x 9 + ischaemic sctroke x 6

	Gram(+)/Gram(-) (n)	Non-Gram(+)/Gram(-) (n)	
Score ≥8	25 Sens= 22.5% PPV= 43.1%	35	60
Score <8	86	352 Spec= 90.9% NPV= 80.4%	438
	111	387	498

OR= 3.01 (95% CIs= 1.75-5.48); p< 0.0001

C)

Score for Gram(-)=
Ulcer x 10 + peptic ulcer x 14 + solid tumor
malignancy x 9

	Gram(-)(n)	Non-Gram(-) (n)	
Score ≥21	5 Sens= 9.8% PPV= 38.5%	8	13
Score <21	46	439 Spec= 98.2% NPV= 90.5%	485
	51	447	498

OR= 5.96 (95% CIs= 1.87-18.98); p: 0.006

Fig. 4. Proposed scores for the likelihood of pathogens based on clinical variables: (A) infection by methicillin-resistant *Staphylococcus aureus* (MRSA); (B) infection by both Gram-positive cocci and Gram-negative bacteria; and (C) infection by Gram-negative bacteria. CI, confidence interval; LTCF, long-term care facility; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

for infections by MRCNS, although recent intake of clindamycin and medical history of chronic obstructive pulmonary disease were the only variables positively associated with the isolation of MRCNS.

4. Discussion

This is the largest cohort study reporting the microbiology of skin infections following the introduction of the recent FDA definition of ABSSI. The main findings are the rate of resistance to methicillin among microbiologically evaluable patients (57.3%), the rate of mixed Gram-positive and Gram-negative infections (27.3%) and the development of three different scoring systems that use clinical variables at presentation of ABSSSI to predict the causative pathogen.

Since the publication of the FDA ABSSSI definition, four randomised clinical trials have been published on the evaluation of the clinical efficacy of two new antistaphylococcal agents, namely dalbavancin and tedizolid. These trials are known by the acronyms DISCOVER and ESTABLISH [7–9]. In these trials, patients with a high likelihood for Gram-negative infection were discouraged from participation, which may explain the substantial predominance of staphylococcal species among their microbiologically evaluable patients. However, the frequency of streptococci as pathogens in these trials was very low and this may explain why streptococci were not found as pathogens in the current cohort. The results of the current study outline that Gram-negative pathogens cannot be underestimated as pathogens for ABSSSIs and that specific clinical criteria are mandatory to drive the clinician towards the likely pathogen, since in almost 40% of cases no microbiological diagnosis is established.

The reported findings corroborate to some extent those reported by others who analysed smaller cohorts before the introduction of the ABSSSI definition. Zervos et al. analysed 1096 hospitalised patients with complicated SSTIs and reported *S. aureus* as the prevailing pathogen in 66.4% of microbiologically evaluable cases, of which the most common isolate was MRSA [10]. *Staphylococcus aureus* remains the most common pathogen in the USA and Australia [11,12], although a decrease has been reported in the USA [11].

A main finding of the current study is that one of the most commonly isolated pathogens was MRCNS. It is not the first time where such a result is reported. Watanabe et al. reported that coagulase-negative staphylococci (CoNS) were implicated in 30% of their cases, where resistance to methicillin of *Staphylococcus epidermidis* and *Staphylococcus lugdunensis* was 55.7% and 12.9%, respectively [13]. The prevalence of CoNS in the European Cubical® Outcomes Registry and Experience (EU-CORE^{SM}) was 28.5% [14]. Bouza et al. reported that among 69 patients receiving at least one dose of dalbavancin for ABSSSI, CoNS was the pathogen in 24 patients [15].

Zilberberg et al. analysed 717 hospitalised patients with complicated SSTIs and reported Gram-negative bacteria as the most common pathogens [16]. The same authors reported a 10.6% prevalence of mixed Gram-positive and Gram-negative infections among healthcare-associated SSTIs. The most common isolates

were *P. aeruginosa, Escherichia coli* and *Klebsiella* spp. These authors reported a lower prevalence of mixed infections than reported in the current study and a greater prevalence of Gram-negative infections. The 2011–2014 analysis of healthcare-associated infections by the National Healthcare Safety Network (NHSN) of the CDC revealed that in the case of surgical site infections, *S. aureus* was the most common pathogen (20.7%), followed by *E. coli* (13.7%), *P. aeruginosa* (5.7%) and *Klebsiella* spp. (4.7%); 42.7% of *S. aureus* isolates were resistant to methicillin [17].

Despite the existence of Gram-negative bacteria in the causality of ABSSSIs, it is beyond any doubt that methicillin-resistant staphylococcal species predominate. Data from US national surveillance systems show that community-associated MRSA clones represent a substantial proportion of pathogens and may even be responsible for the majority of healthcare-associated infections caused by MRSA [18]. The current analysis indicated hospitalisation in the last 90 days and residency in a LTCF as independent predictors of MRSA, as also described by others [19]. Since MRSA also predominated among patients infected by both Gram-positive cocci and Gram-negative bacteria, it is not a surprise that residency in a LTCF is part of the prediction scores for monomicrobial MRSA and for mixed Gram-positive and Gram-negative infections. The other elements of the scores (i.e. atrial fibrillation and stroke for monomicrobial MRSA, and infection in the lumbar area, fluoroquinolone intake and stroke for mixed Gram-positive and Gram-negative infections) are novel.

Three main limitations of the study should be acknowledged. (i) Analysis was based on the screening results of the randomised AIDA trial and this may have led to some selection bias, e.g. exclusion of patients receiving haemodialysis. (ii) The use of cotton swabs for sampling cultures. However, this technique, when done appropriately, provides concordance with tissue specimens as high as 78% [20]. And (iii), the lack of using another broad growth medium such as blood agar in parallel with MacConkey agar, MSA and CHROMagar for the culture of pus samples, making it possible that some isolates could have been missed. Despite the addressed limitations, the present study goes well beyond the traditional epidemiological analysis of prevalence of pathogens and their resistance rates in ABSSSIs as it is the first time where precise patient characteristics are combined into separate scores to assist prediction of the likelihood of specific pathogens with specificity >90%.

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Competing Interests: EJG-B has received honoraria (paid to the University of Athens, Athens, Greece) from AbbVie USA, Abbott CH, Biotest Germany, Brahms GmbH, InflaRx GmbH, the Medicines Company, MSD Greece and XBiotech Inc., has received independent educational grants from AbbVie, Abbott, Astellas Pharma, Axis Shield, bioMérieux Inc., InflaRx GmbH, the Medicines Company and XBiotech Inc., and has received funding from the FrameWork 7 program HemoSpec and from the Horizon2020 Marie-Curie project European Sepsis Academy (granted to the National and Kapodistrian University of Athens, Athens, Greece); AM receives grant income from Motif Bio, InfectoPharm, Paratek, Merck, VenatoRx Pharmaceuticals and Wockhardt, is part of IMI-funded programmes including AiCuris, The Medicines Company, MedImmune and Evotec, and receives grants from MRC (UK) and NIHR (UK). All other authors declare no competing interests.

Ethical approval: The study protocol was approved by the Ethics Committees of the hospitals of the participating study sites, by the National Ethics Committee of Greece and by the National Organization for Medicines of Greece [approval 87/14].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.08.020.

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