Pathogens of skin and skin structure infections in the UK and their susceptibility to antibiotics, including ceftaroline

DAVID M LIVERMORE[1,2*], SHAZAD MUSHTAQ[1], MARINA WARNER,[1] DOROTHY JAMES,[1] ANGELA KEARNS[1] AND NEIL WOODFORD[1]

[1]*Antimicrobial Resistance and Healthcare Associated Infections Reference Unit, Public Health England, 61 Colindale Avenue, London, NW9 5EQ*

[2]*Norwich Medical School, University of East Anglia, Norwich, NR4 7JT*

***Corresponding author:**

Norwich Medical School, University of East Anglia, Norwich, NR4 7JT

Tel +44-(0)1603-597-568; d.livermore@uea.ac.uk

Running Heads

SSSI epidemiology and ceftaroline in the UK

Keywords

MRSA, *Staphylococcus aureus*, ceftaroline, skin infection, susceptibility testing

Background. Bacterial skin and skin structure infections (SSSIs) are frequent settings for antibiotic use. We surveyed their UK aetiology and pathogen susceptibility, including to ceftaroline. **Materials and Methods.** Consecutive SSSI isolates were collected at 35 UK hospitals, to a maximum of 60/site, together with 15 'supplementary' MRSA/site. Isolates were re-identified and BSAC susceptibility testing performed, with parallel CLSI agar testing for ceftaroline. **Results**. Isolates (n=1908) were collected from 1756 hospitalised patients, predominantly with surgical and traumatic infections, abscesses and infected ulcers and primarily from General Medicine and General Surgery. They included 1271 *Staphylococcus aureus* (201 MRSA), 162 β-haemolytic streptococci, 269 Enterobacteriaceae, 138 *Pseudomonas aeruginosa* and 37 enterococci. Most (944/1756) patients had monomicrobial MSSA infections. Resistance rates to quinolones, gentamicin and cephalosporins were <20% in Enterobacteriaceae and <10% in *P. aeruginosa*. MRSA rates varied greatly among hospitals and were 2.5-fold higher in General Medicine than General Surgery. At breakpoint, ceftaroline inhibited (i) all MSSA and 97.6% of MRSA, with MICs of 2 mg/L for the few resistant MRSA, (ii) all β-haemolytic streptococci and (iii) 83% of Enterobacteriaceae. High-level ceftaroline resistance in Enterobacteriaceae involved ESBLs and AmpC enzyme. Ceftaroline MICs by CLSI methodology generally equalled those by BSAC or were two-fold higher, but this differential was 4-16-fold for *P. aeruginosa*. **Conclusion.** Irrespective of patient group, SSSIs were dominated by *S. aureus*. Most pathogens were susceptible; but 15.8% of *S. aureus* were MRSA, with locally higher prevalence.

Introduction

Skin and skin structure infections (SSSIs, or 'Acute Bacterial Skin and Skin Structure Infections' or ABSSSI in FDA terminology[1]) range from trivial to the life threatening. They are important in both hospitals and the community, with categorisation complicated by the fact that hospital acquired (e.g. post-surgical) SSSIs increasingly manifest in the community, following early hospital discharge.[2] Regulatory agencies divide SSSIs as 'complicated' or 'uncomplicated' according to the depth of the structures involved, but routine practice mostly categorised by type (cellulitis, surgical site *etc.*). SSSI aetiology is dominated by *Staphylococcus aureus* but other common isolates include β-haemolytic streptococci, enterococci, Enterobacteriaceae, anaerobes and *Pseudomonas aeruginosa.*[3] In a mixed flora, it is often difficult to distinguish pathogens and secondary colonists with confidence.

There is great variation in SSSI treatment, with 54 antibiotic regimens represented among 1995 SSSI patients at 129 hospitals.[4] Severity varies hugely too, with UK evidence suggesting that severe SSSIs are frequently undertreated, sometimes with adverse consequences, whereas mild infections are often over-treated.[5] Guiding principles are that the regimen should reflect: (i) the likelihood of a mixed flora, including gram-negatives; (ii) the prevalence of MRSA and (iii), severity, along with the consequences of failure. The prevalence of MRSA among bloodstream infections in the UK has been substantially reduced, but their residual prevalence in SSSIs is less clear. Multiple antibiotics – ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin-dalfopristin, tedizolid, and tigecycline – have been licensed for SSSIs since the turn of the century, all with anti-MRSA activity.[6] Most only act against gram-positive pathogens but ceftaroline and tigecycline, also inhibit Enterobacteriaceae, but not *P. aeruginosa*.

We surveyed the current aetiology of SSSIs among hospitalised patients in the UK, considering MRSA prevalence in particular. In addition we ascertained (i) the coverage offered by ceftaroline and (ii) the extent to which the MIC distribution for MRSA is cut by EUCAST's 1 mg/L breakpoint (http://www.eucast.org).

Materials and methods

SSSI survey

We recruited 40 UK laboratories, asking each to collect 60 consecutive clinically-significant isolates from hospitalised patients with SSSI and to send these to Public Health England's Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI). Collection ran from August 2012 to December 2013, and 35 sites contributed isolates (See Acknowledgements); 29 were in England, three in Scotland, two in Wales and one in Northern Ireland. Bacteria sought included *S. aureus*, β-haemolytic streptococci, enterococci, Enterobacteriaceae or non-fermenters. Anaerobes were excluded, as were: (i) commensal species likely to be contaminants, including coagulase-negative staphylococci, micrococci, propionibacteria and coryneforms, (ii) α-haemolytic staphylococci and (iii) category III pathogens. Only one isolate per species per patient was permitted, except that MRSA and MSSA could be included. A case record form was sought for each isolate, collecting demographic and clinical data.

To expand the MRSA collection we also asked laboratories to submit a further 15 MRSA from SSSIs subsequent to their collection of 60 consecutive isolates.

Identification and susceptibility testing

Isolates were re-identified at AMRHAI as follows: *S. aureus* with Chromagar *Staph aureus* (Chromagar, Paris, France) and PCR for *mecA*;[7] β-haemolytic streptococci by Lancefield typing using Streptococcal Grouping Latex Kits (Pro-Lab Diagnostics, Merseyside, UK); enterococci and gram-negative bacilli by MALDI-ToF mass spectrometry (MALDI Biotyper, Bruker, Coventry, UK). MICs were determined by BSAC agar dilution on IsoSensitest agar (Oxoid-Thermofisher, Basingstoke, UK),[8] except that Isotonic agar with 50 mg/L Ca^{2+}(Mast Laboratories, Bootle, UK) was used for daptomycin. Results were graded *vs.* EUCAST breakpoints (http://www.eucast.org), which have been adopted by the BSAC.[9] Ceftaroline MICs additionally were determined by CLSI agar dilution[10] on Mueller Hinton agar (Oxoid).

Enterobacteriaceae found non-susceptible to ceftaroline (MIC >0.5 mg/L) and/or cefotaxime (MIC >1 mg/L) were subjected to ESBL tests, using BSAC agar dilution methodology to seek synergy between clavulanate 4 mg/L and cefepime, cefotaxime, ceftaroline or ceftazidime.

Antibiotic powders were obtained from suppliers as follows: ceftaroline (AstraZeneca, Macclesfield, UK), clavulanate (GlaxoSmithKline, Brentwood, UK) daptomycin (Novartis, Basel, Switzerland), linezolid and tigecycline (Pfizer, Sandwich, UK), cefepime (USP, Rockville, USA); quinupristin and dalfopristin (Nordic Pharma, Theale, UK); ampicillin, benzylpenicillin, cefotaxime, ceftazidime, ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, tetracycline, teicoplanin, vancomycin (Sigma, Poole, UK).

Typing of S. aureus

MRSA with ceftaroline MICs ≥2 mg/L were *spa*-typed as described by Harmsen *et al.*[11] with types assigned via the Ridom GmbH spa website, http://www.spaserver.ridom.de. Multi Locus Sequence Type Clonal Complex (MLST-CC) assignments were inferred using the *spa* server (http://spa.ridom.de/mlst.shtml) and MLST database (http://saureus.mlst.net).

Results

The 35 laboratories contributed 11-60 isolates each, with a mean of 50 isolates/site and a total of 1908 consecutive organisms received. These were from 1756 patients: 1538 (87.4%) with a single pathogen and 219 (12.6%) with two or more pathogens; the latter total includes patients noted as co-infected with anaerobes, although these were not collected. We also received 329 supplementary MRSA. As these lacked denominator data, they were used only to add robustness to MIC distributions, and were excluded from epidemiological analyses.

Patient demographics and infection types

The 1756 source patients for the consecutive isolates comprised 918 men and 838 women; 35 aged 18-20 years; 131 from 21-30 years; 152 from 31-40 years; 189 from 41-50 years; 224 from 51-60 years; 281 from 61-70 years; 327 from 71-80 years; 308 from 81-90 years

and 109 aged 91 years or older. Patients with MRSA averaged 5 years older (66.1 years, SD 19.9 years) than those with MSSA (61.4 years, SD 21.7 years). Referring specialities (Table 1) were dominated by General Medicine and General Surgery, each accounting for around one quarter of patients. Accident and Emergency/Admissions Unit, Care of the Elderly, and Orthopaedic Surgery accounted for a further 7.6-15.2% of patients. Only 4.4% of patients were in intensive care. Patients' infection types are summarised in Table 2: 46.4% had surgical, traumatic or other wounds, whilst 16% had ulcers or sores and 11.3% had abscess infections. Among smaller groups, 3.8% of patients had infected burns whilst 4.4% had diabetes-related lower extremity infections. Swabs were the dominant specimen type, from 1617/1756 (92%) patients; other samples included pus (n= 73), tissue (n=36), fine needle aspirates (n=14) and catheter tips (n=10).

Pathogens in relation of hospital site and infection type

S. aureus dominated, being present in 72.4% of infections sampled and the sole pathogen in 64.7%. It was present in 60-100% of infections in each hospitalisation category and each infection site (Tables 1 and 2); and was the sole pathogen in ≥57% infections at each infection site and in all settings except intensive care (47%). Fully 944/1756 (53.8%) of patients had infections solely involving MSSA. MRSA accounted for 15.8% of *S. aureus*, with proportions exceeding 20% in General Medicine, Neurology and Nephrology/Renal patients and among *S. aureus* isolates from infected lines, infected sores and 'other' wounds. No MRSA were recovered from Haematology/Oncology or (unsurprisingly) Obstetrics-Gynaecology patients and proportions were below 10% among *S. aureus* from Burns Units and burn infections, General Surgery and surgical site infection. The MRSA rate among *S. aureus* isolates from General Medicine Patients (22.8%) was 2.5x that (9.3%) among General Surgery patients, with this excess substantially reflecting large numbers of MRSA from traumatic wounds and infected ulcers and sores – groups where the MRSA proportion exceeded 20%. There was little major clustering when hospital site and infection type were combined (Table 3), but it is notable that more than half the General Medicine MRSA were

from ulcers and 'other (i.e. non-surgical) traumatic wounds. MRSA proportions among *S. aureus* varied greatly with the hospital, from 0-68%: 10 sites had rates below 10%; 15 had rates 10-20%, five had rates 20-30% and five had rates >30%. These last five, two of them in Wales, accounted for 72/201 of the MRSA collected (36%). Their distribution of clinical and ward/unit sites for MRSA resembled the generality of hospitals (now shown), suggesting that these excesses did not reflect different sampling approaches. Among the 201 MRSA patients, 192 had MRSA as the sole pathogen and only nine had MRSA in mixed infections, three with *P. aeruginosa* and three with 'unknown' pathogens.

No other pathogen group besides *S. aureus* was recovered from more than 15% of all patients. Enterobacteriaceae (n=269) included 125 *E. coli*, 38 *Enterobacter* spp., 34 *Proteus mirabilis* and 34 *Klebsiella/Raoultella* spp., 14 *Serratia* spp. 13 *Citrobacter* spp. and 11 indole-positive Proteeae, and were recovered from 252 patients (14.4%, with 17 having multiple species). In 179/252 cases (70.1%), Enterobacteriaceae were the sole pathogens; in the remainder they were co-present with other pathogens, predominantly *S. aureus*. Enterobacteriaceae were most frequent in General and Orthopaedic Surgery and Intensive Care Patients, being present in over 20% of surgical site infections, abscesses and (more surprisingly) line infections, but in fewer than10% of traumatic wound infections, infected ulcers, infected burns and infected dermatological conditions.

Streptococci were submitted from 9.3% of patients; most were Lancefield B, C, G organisms (n=137) not *S. pyogenes* (n=26). Prevalence was greatest in Accident and Emergency/Admissions Unit and Care of the Elderly patients and from infected ulcers and sores, cellulitis, infected dermatological conditions and diabetic lower extremity infections. Fewer than half (65/137) of the B, C, G streptococci were from monomicrobial infections *versus* two-thirds (17/26) of the *S. pyogenes* isolates.

P. aeruginosa was recovered from 138 patients (7.9%) and was sole pathogen in 102. Rates were highest in ICU, renal, cardiothoracic surgery and haematology/oncology

patients, whereas the prevalence rate in Burns Unit (4.2%) and burn infections (6.1%) were low, despite the organism's predilection for this milieu.[12] Settings where *P. aeruginosa* was submitted from over 10% of cases included line infections, 'other' wound infections, diabetic lower extremity infections and cellulitis. Enterococci (30 *E. faecalis*, 16 *E. faecium* and one *E. raffinosus*) were submitted from 37 (2.7%) of patients and were sole pathogens in 27. Proportions of patients with enterococci were highest (6.1-8.3%) in burn infections and Burns Units; settings with the highest rates were unrelated to those with the highest Enterobacteriaceae rates, despite both being gut organisms with the same likely origin.

Antibiotic susceptibility

Susceptibility data are summarised by species group in Tables 4-6 with ceftaroline MIC distributions shown in Table 7. MSSA -accounting for 56.1% of all isolates- were very susceptible, with even erythromycin and tetracycline active *vs*. >85% of isolates (Table 4). MRSA were mostly resistant to erythromycin and ciprofloxacin but were otherwise susceptible, as typical of the EMRSA-15/CC22 and EMRSA-16/CC30 MRSA lineages predominant in the UK.[13] Daptomycin, linezolid, tigecycline and glycopeptides were active against >99% of both MRSA and MSSA. Ceftaroline, 1 mg/L was active against all MSSA irrespective of method, and against 97.5% of the MRSA by BSAC methodology or 94.0% by CLSI methodology. These latter proportions trivially altered to 98.0% and 95.1%, respectively, when the supplementary MRSA were included (Table 7). MICs for all the ceftaroline non-susceptible MRSA were 2 mg/L, representing the upper tail of a unimodal distribution, and counting as resistant by EUCAST criteria, though intermediate on those of the CLSI and FDA. The 25 MRSA with MICs of 2 mg/L by CLSI methodology included all eight with MICs 2 mg/L by the BSAC method. Twenty-three were *spa*-typed and all except one belonged to types corresponding to EMRSA-15/CC22 (n=10, *spa* types t022, t023, t032, t906, t747, t1977 and t3213) or EMRSA-16/CC30 (n=12, *spa* types t012, t018, t253); the exception was a CC5 *spa* t045 isolate.

All streptococci were susceptible to penicillin, ceftaroline, daptomycin, linezolid, tigecycline and glycopeptides (Table 4). Resistance was only frequent to tetracycline (especially for Group B /*Streptococcus agalactiae*) and erythromycin. MICs of ceftaroline were tightly clustered and unimodal, with values from 0.002-0.015 mg/L (Table 7). Within this range, values were highest for Group B / *S. agalactiae* and lowest for *S. pyogenes*. Among enterococci (Table 5), 50% of *E. faecalis* and 33.3% of *E. faecium* had high-level gentamicin resistance and half the *E. faecium* isolates had glycopeptide resistance, always corresponding to the VanA phenotype, with both vancomycin and teicoplanin compromised. These high rates must be set against the overall infrequency of enterococci, which comprised less than 2% of the collection. With one exception (MIC, 4 mg/L) *E. faecium* isolates were highly resistant to ceftaroline but 25/30 *E. faecalis* were inhibited at 0.25-1 mg/L, with MICs of 4-8 mg/L for the remaining five. Bimodal MIC distributions were noted previously for *E. faecalis* with anti-MRSA cephalosporins, but remain unexplained.[14]

E. coli comprised almost half the Enterobacteriaceae collected (125/269, 46.4%), with *Enterobacter* spp., *Klebsiella* spp. and *P. mirabilis* each comprising 12.5-14.1%. Most of the resistance seen was of types inherent to particular species or genera (Table 6). Thus *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia* and indole-positive Proteeae mostly were resistant to ampicillin *Citrobacter freundii*, *Enterobacter*, *Serratia* and *Morganella morganii* to co-amoxiclav. Over 85% of isolates of each species were susceptible to gentamicin and ciprofloxacin. The behaviour of cephalosporins was more complex, and was investigated for all 45 isolates with ceftaroline MICs >0.5 mg/L. These divided into three groups (Table 8). The first comprised 15 isolates – mostly *E. coli* and *K. pneumoniae* – deduced to have ESBLs based on synergy between all cephalosporins and clavulanate. These were all were substantially resistant to ceftaroline, with MICs >16 mg/L and to cefotaxime; many were also multiresistant to gentamicin and cirprofloxacin. The second group comprised 16 isolates – mostly *Enterobacter*, *C. freundii*, *M. morganii* and *Serratia* – with greater resistance to cefotaxime, ceftazidime and ceftaroline than to cefepime, to which 13/16 remained susceptible. Cephalosporin MICs for these isolates were not reduced by clavulanate. This

combination of cefepime susceptibility and clavulanate-independent resistance implied high-level AmpC activity. MICs of ceftaroline for these isolates ranged from 2->256 mg/L with 13/16 values ≥8 mg/L. The final group of 14 isolates had low-level ceftaroline resistance (MIC 1-16 mg/L) and were susceptible to the other three cephalosporins or had only intermediate resistance, with MICs never exceeding 2 mg/L: six were *E. coli* and six were *Serratia* spp.; ceftaroline MICs for the *E. coli* isolates were reduced by clavulanate to ≤0.12 mg/L; those for the *Serratia* spp. were raised by clavulanate in many cases, implying AmpC induction. Overall, ceftaroline retained activity *vs.* 83.3% of Enterobacteriaceae isolates, with over 80% susceptibility except among *Enterobacter* (68.4%) and *Serratia* spp. (35.4%). No Enterobacteriaceae were non-susceptible to cefotaxime but susceptible to ceftaroline.

For *P. aeruginosa*, susceptibility rates to ceftazidime, gentamicin and ciprofloxacin all exceeded 90%, confirming the pattern of infrequent resistance outside chronic respiratory infections that is typically seen in the UK.

Ceftaroline MICs by BSAC vs CLSI methodology

Ceftaroline MICs of 2 mg/L were found for a greater, but still small, proportion of MRSA by CLSI methodology than by BSAC methodology (Table 7). This followed a wider pattern whereby, in >97% of cases excluding *P. aeruginosa*, MICs of ceftaroline by CLSI methodology on equalled those on IsoSensitest agar, or were two-fold higher (Table 9). For *P. aeruginosa* the differential was 4-16-fold; reasons are unclear and the point is academic, since the species is universally agreed to be resistant, with no breakpoints assigned.

Discussion

We sought to define the current aetiology of SSSIs in the UK, the residual prevalence of MRSA, and the activity of ceftaroline. The study aimed to provide a large snapshot, but two caveats should be noted: (i) recording of ward type by participating laboratories is probably more accurate than recording of infection type, since laboratories know where a specimen

has come from, but depend on the ward for information about the type of infection and (ii) we depended on laboratories' categorisation of organisms as pathogens. The proportion of SSSIs categorised as polymicrobial (12.6%) was lower than found by others – e.g. 41.4% in a 134-hospital, 12,506-patient US survey[3] and 22.8% in Phase III trials with ceftaroline.[15] This may reflect differing 'norms' in recording secondary organisms, also our exclusion of coagulase-negative staphylococci, which were included as pathogens or co-pathogens in some surveys though not generally in Phase III SSSI data. Despite these caveats, the unit and clinical site analyses presented in Tables 1 and 2 are mutually consistent with similar aetiology across e.g.: (i) surgical site infections and the General and Orthopaedic Surgery groups, and between burn infections and Burns Unit patients.

The species distributions, with *S. aureus* dominating in all subsets agrees with that reported by Lipsky *et al.*[3] though percentages differ partly because Lipsky *et al.* accepted CoNS as significant, to the extent of including them as the sole pathogens in 18.2% of infections. *S. aureus* was sole pathogen in 54.7% of Lipsky's monomicrobial SSSIs, rising to 66.8% if CoNS were discounted, compared with 64.7% here. Proportions of monomicrobial infections with Enterobacteriaceae, streptococci (pooled), *P. aeruginosa* and enterococci were 10.1%, 9.5%, 3.1% and 3.5%, respectively, in Lipsky's series, rising to 12.3%, 11.6%, 3.8% and 4.3% once CoNS were disregarded, compared with 10.1%, 4.7%, 5.8, 1.5% here. Another study of 527 patients with healthcare-associated cSSSI,[16] found *S. aureus* in 48.6%, enterococci in 14.6% and *P. aeruginosa* in 10.1%, whilst the SENTRY surveillance found that *S. aureus* accounted for 45.9% of SSSI pathogens and *P. aeruginosa* for 10.8%.[17] Recent Phase III antibiotic trials in complicated SSSI/ABSSSI trials[18,19] again show a similar distribution, with *S. aureus* in more than half the patients and with β-haemolytic streptococci, *P. aeruginosa* and Enterobacteriaceae in 5-20% each versus enterococci in under 5%. The one radically different report is Public Health England's surgical site surveillance for English hospitals 2013-4,[20] which indicates a much lower proportion of *S. aureus* (16% or 18.4%, if rebased to exclude CoNS), with Enterobacteriaceae dominant (26%, or 30% if rebased to

exclude CoNS). The dominance of Enterobacteriaceae derived from their high proportion (56.7%) in infection following bowel surgery, where only 13.0% of patients had *S. aureus. S. aureus* remained the major pathogen in the PHE orthopaedic surgery series, present in 54.5%-64.3% of monomicrobial infections. The difference between the low rate of *S. aureus* in the PHE bowel surgery series and the high rate in the present General Surgery group (which should heavily represent bowel surgery) remains unexplained.

Asides from underscoring the dominance of *S. aureus*, the present analysis importantly shows: (i) that SSSIs in ICUs had a more diverse aetiology than those in other patient groups, with Enterobacteriaceae and *P. aeruginosa* more prevalent; (ii) that Enterobacteriaceae were also prominent in General and Orthopaedic Surgery patients, and in their surgical site infections; (iii) that, more surprisingly, Enterobacteriaceae were prevalent in line infections and (iv) that streptococci, which were mostly B, C, G types, were most prevalent in Emergency and Admissions Unit patients and Care of the Elderly and in cellulitis, whereas Enterobacteriaceae were rare pathogens in Emergency and Admissions Unit SSSI patients and Care of the Elderly. Such data, together with information on MRSA prevalence, point to settings where broad-spectrum therapy may be desirable in the empirical management of SSSIs. Ceftaroline may have a particular potential in mixed SSSIs that involve MRSA together with Enterobacteriaceae, but these are now rare in the UK: only 9/201 MRSA were from mixed infections and these largely had 'unknowns' or *P. aeruginosa* as the second isolate, not Enterobacteriaceae.

Rates of resistance were low. Fully 944/1756 patients had monomicrobial MSSA infections. Only 15.8% of *S. aureus* isolates were MRSA and among General Surgery patients, the MRSA rate was <10%. This contrasts with a 61% MRSA rate among *S. aureus* from surgical site infections in England in 1997-9[21] and doubtless reflects the success of subsequent MRSA reduction programmes, which have also seen a >85% reduction in MRSA bacteraemias in England since their 2003/4 peak.[22,23] Other settings where MRSA rates were below 10% included Burns Units, Obstetrics and Gynaecology and Haematology-

Oncology; an ICU MRSA rate of only 12.5% contrasts with 51.2% among SSSI ICU *S. aureus* in 2001[24]. The higher MRSA rate in General Medicine –two and a half times that in General Surgery– was associated with infected ulcers and 'Other' traumatic wounds (Table 3). The proportion of MRSA was higher particular hospitals, with 5/35 hospitals accounting for 35% of MRSA. Two of these five sites were in Wales, which had risk-based pre-admission MRSA screening during the survey period than universal screening, as then applied in England Among other common pathogens, streptococci were universally susceptible, except to tetracycline and erythromycin whilst over 90% of Enterobacteriaceae were susceptible to ciprofloxacin and gentamicin and over 80% were susceptible to cephalosporins. Over 90% of *P. aeruginosa* were susceptible to ciprofloxacin, gentamicin and ceftazidime.

Fully 97.5% (98.3% with supplementary isolates) of collected MRSA were susceptible to ceftaroline by BSAC methodology, with this proportion falling to 94.0% (95.1%) by CLSI methodology. Typing found little exceptional about the resistant isolates, which almost all belonged to the EMRSA-15/CC22 and EMRSA-16/CC30 lineages that have long dominated among HA-MRSA in the UK.[3,25] MICs never exceeded 2 mg/L, whereas values of 4 mg/L have been seen for small minorities of isolates in Greece and Germany, with some of these being shown to harbour PBP2' mutations.[26,27] Predictably, ceftaroline lacked activity against Enterobacteriaceae that were resistant to cefotaxime and which had profiles indicating ESBLs or derepressed AmpC. Resistance was seen also in a few further Enterobacteriaceae that lacked clear resistance to other cephalosporins; these predominantly comprised *E. coli* with ceftaroline/clavulanate synergy and *Serratia* spp. with ceftaroline MICS of 1 mg/L; the former group is in keeping with the observation that high-level expression of classical TEM enzymes confers low-level protection against ceftaroline,[14] the second simply reflects *Serratia* spp. being inherently less susceptible than other Enterobacteriaceae (mode MIC 1 mg/L *vs*. 0.12-0.25 mg/L for other genera, Table 6), with the tail of the normal distribution thus being cut by the breakpoint.

In summary, these data provide a snapshot of the aetiology of SSSIs in the UK, indicating the dominance of MSSA and the settings where MRSA is now concentrated. In most cases, multiple treatment options remain and narrow-spectrum anti-gram-positive therapy is appropriate. Ceftaroline offers potential in the now less common situation where combinations of MRSA and Enterobacteriaceae are present.

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References

1. Itani KM, Shorr AF. FDA guidance for ABSSSI trials: implications for conducting and interpreting clinical trials. *Clin Infect Dis* 2014;**58 Suppl 1:**S4-9
2. Leaper D, Tanner J, Kiernan M. Surveillance of surgical site infection: more accurate definitions and intensive recording needed. *J Hosp Infect* 2013;**83:**83-6.
3. Lipsky BA, Weigelt JA, Gupta V *et al.* Skin, soft tissue, bone, and joint infections in hospitalized patients: epidemiology and microbiological, clinical, and economic outcomes. *Infect Control Hosp Epidemiol* 2007;**28:**1290-8.
4. Garau J, Ostermann H, Medina J *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
5. Marwick C, Broomhall J, McCowan C *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.
6. Dryden MS. Novel antibiotic treatment for skin and soft tissue infection. *Curr Opin Infect Dis* 2014;**27:**116-24
7. Bignardi GE, Woodford N, Chapman A *et al.* Detection of the *mecA* gene and phenotypic detection of resistance in *Staphylococcus aureus* isolates

with borderline or low-level methicillin resistance. *J Antimicrob Chemother* 1996;**37:**53-63.

8. Anon. A guide to sensitivity testing. Report of the Working Party on Antibiotic Sensitivity Testing of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 1991**;27 Suppl D**:1-50.

9. Howe RA, Andrews JM; BSAC Working Party on Susceptibility Testing. BSAC standardized disc susceptibility testing method (version 11). *J Antimicrob Chemother* 2012;**67:**2783-4.

10. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard M07-A9 —Ninth Edition*. CLSI, Wayne, Pa. 2012.

11. Harmsen D, Claus H, Witte W *et al.* Typing of methicillin-resistant *Staphylococcus aureus* in a university hospital setting by using novel software for *spa* repeat determination and database management. *J Clin Microbiol* 2003;**41:**5442–5448.

12. Azzopardi EA, Azzopardi E, Camilleri L *et al*. Gram-negative wound infection in hospitalised adult burn patients-systematic review and metanalysis. *PLoS One* 2014;**9:**e95042.

13. Ellington MJ, Hope R, Livermore DM *et al.* Decline of EMRSA-16 amongst methicillin-resistant *Staphylococcus aureus* causing bacteraemias in the UK between 2001 and 2007. *J Antimicrob Chemother* 2010;**65:**446-8.

14. Mushtaq S1, Warner M, Ge Y *et al.* In vitro activity of ceftaroline (PPI-0903M, T-91825) against bacteria with defined resistance mechanisms and phenotypes. *J Antimicrob Chemother* 2007;**60:**300-11.

15. Corey GR, Wilcox M, Talbot GH *et al.* Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 2010;**51:**641-50.

16. Zilberberg MD, Shorr AF, Micek ST *et al.* Epidemiology and outcomes of hospitalizations with complicated skin and skin-structure infections: implications of healthcare-associated infection risk factors. *Infect Control Hosp Epidemiol* 2009;**30:**1203-10.

17. Rennie RP, Jones RN, Mutnick AH. SENTRY Program Study Group (North America).Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). *Diagn Microbiol Infect Dis* 2003;**45:**287-93.

18. Friedland HD, O'Neal T, Biek D *et al.* CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother* 2012;**56:**2231-6.

19. Breedt J, Teras J, Gardovskis J *et al.* Tigecycline 305 cSSSI Study Group Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. *Antimicrob Agents Chemother* 2005;**49:**4658-66.

20. Anon. Surgical site infections (SSI) surveillance: NHS hospitals in England. Public health England, available via https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/386927/SSI_report_2013_14_final__3_.pdf. Date last accessed, 27th March, 2015

21. Pearson AD. Reports on surgical site infections and hospital acquired bacteraemias from the Nosocomial Infection National Surveillance Scheme. Eurosurveillance, Volume 4, Issue 24, 15 June 2000. Available via http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=1582. Date last accessed, 27th March, 2015

22. Pearson A, Chronias A, Murray M. Voluntary and mandatory surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia in England. *J Antimicrob Chemother* 2009;**64 Suppl 1:**i11-7.

23. Johnson AP, Davies J, Guy R, *et al*. Mandatory surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in England: the first 10 years. *J Antimicrob Chemother* 2012;**67:**802-9

24. Johnson AP, Henwood C, Mushtaq S *et al.* Susceptibility of gram-positive bacteria from ICU patients in UK hospitals to antimicrobial agents. *J Hosp Infect* 2003;**54:**179-87.

25. Enright MC, Day NP, Davies CE *et al.* Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus. J Clin Microbiol* 2000;**38:**1008-15.

26. Mendes RE, Tsakris A, Sader HS *et al*. Characterization of methicillin-resistant *Staphylococcus aureus* displaying increased MICs of ceftaroline. *J Antimicrob Chemother* 2012;**67:**1321-4.

27. Strommenger B, Layer F, Klare I, Werner G. Pre-use susceptibility to ceftaroline in clinical *Staphylococcus aureus* isolates from Germany: is there a non-susceptible pool to be selected? *PLoS One* 2015;**10:**e0125864.

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Table 1. Organisms isolated in relation to hospital site

% involving	Gen Med	Gen Surg	A&E/ Adm	CoE	Ortho	ICU	CTS	Burns unit	OB-GYN	Haem Onc	Neph/ Renal	Other /NR	Derm	Neuro	Over-all %
S. aureus	75.1	64.6	80.8	81.2	67.9	51.3	65.0	85.4	71.0	75.9	62.1	83.3	100.0	83.3	72.4
β-Streptococci, A,B,C,G	9.1	8.7	16.1	13.3	4.5	3.8	6.7	6.3	9.7	0.0	0.0	4.2	0.0	8.3	9.3
S. pyogenes	1.4	1.1	1.9	1.8	1.5	1.3	0.0	2.1	3.2	0.0	0.0	0.0	0.0	0.0	1.4
Enterococci	0.9	3.4	1.9	1.8	3.0	6.4	5.0	8.3	3.2	0.0	7.1	4.2	0.0	8.3	2.7
Enterobacteriaceae	11.0	24.1	4.6	6.1	20.1	30.8	15.0	6.3	16.1	13.8	10.3	8.3	0.0	0.0	14.4
P. aeruginosa	9.1	6.7	6.5	6.7	7.5	16.7	11.7	4.2	3.2	10.3	13.8	4.2	0.0	8.3	7.9
1 pathogen	88.8	85.1	84.7	87.3	94.8	79.5	85.0	91.7	96.8	100.0	93.1	91.7	92.3	83.3	87.6
>1 pathogen	11.2	14.9	15.3	12.7	5.2	20.5	15.0	8.3	3.2	0.0	3.4	8.3	7.7	16.7	12.4
S. aureus only	67.1	57.7	68.2	70.3	64.9	47.4	58.3	79.2	67.7	75.9	62.1	75.0	92.3	75.0	64.7
MRSA as % *S. aureus*	22.8	9.3	14.7	18.7	19.8	12.5	15.4	4.9	0.0	0.0	22.2	25.0	15.4	20.0	15.8
Total patients included	**438**	**435**	**261**	**165**	**134**	**78**	**60**	**48**	**31**	**29**	**28**	**24**	**13**	**12**	**1756**

Abbreviations A&E Adm, Accident and Emergency/Admissions Unit; Burns, Burns Unit; CTS, Cardiothoracic Surgery; CoE, Care of Elderly; Derm, Dermatology; Gen Med, General medicine; Gen Surg, General Surgery; Haem Onc, Haematology/Oncology; ICU, Intensive Care Unit; Neph/Renal, Nephrology or Renal Unit; Neuro, Neurology; OB-GYN, Obstetrics/Gynaecology; Ortho, Orthopaedic, NK, not reported

Table 2. Pathogen distribution in relation to type of SSSI

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% involving	Surg site inf	Traum wound inf.	Inf ulcer	Abs-cess	Other/ NR	Cellu-litis	Diab-. related LE inf.	Inf burn	Other wound inf	Line inf	Inf. sore	Inf derm cond	Over-all %
S. aureus	60.9	82.1	77.5	67.3	75.8	76.8	66.7	84.8	81.5	61.7	75.7	92.6	72.4
β-Streptococci, A,B,C,G	4.8	8.8	16.8	9.5	11.4	14.7	14.1	4.5	3.7	0.0	8.1	18.5	9.3
S. pyogenes	0.5	1.3	1.2	3.5	2.0	2.1	3.8	1.5	0.0	0.0	0.0	3.7	1.5
Enterococci	3.9	1.0	0.8	4.5	0.7	2.1	5.1	6.1	3.7	3.3	5.4	0.0	2.7
Enterobacteriaceae	27.5	6.5	4.9	20.6	8.7	10.5	14.1	4.5	5.6	20.0	13.5	3.7	14.4
P. aeruginosa	8.9	5.9	8.2	3.5	8.1	11.6	11.5	6.1	11.1	15.0	8.1	3.7	7.9
1 pathogen	89.3	92.5	83.6	86.9	89.3	78.9	84.6	87.9	85.2	90.0	83.8	77.8	87.6
>1 pathogen	10.7	7.5	16.4	13.1	10.7	21.1	15.4	12.1	14.8	10.0	16.2	22.2	12.4
S. aureus only	57.0	75.9	65.6	61.3	67.1	60.0	59.0	77.3	66.7	58.3	67.6	74.1	64.7
MRSA as % *S. aureus*	9.3	19.4	17.5	17.2	16.8	12.3	15.4	7.1	29.5	21.6	25.0	12.0	15.8
Grand total (n)	**440**	**307**	**244**	**199**	**149**	**95**	**78**	**66**	**54**	**60**	**37**	**27**	**1756**

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483 **Abbreviations** Inf. Burn, infected burn; Inf derm cond, infected dermatological condition; Inf Sore, infected sore; Inf Ulcer, infected ulcer; Line inf, line

484 infection; Other wound inf, other wound infection; NR, not reported; Surg site inf, surgical site infection; Traum. Wound inf, traumatic wound infection;

485 Diab-related LE infection, diabetes related lower extremity infection

Table 3. Distribution of MRSA *vs*. MSSA by infection type and hospital speciality

Row Labels	A&E/ Adm	Burns	CTS	CoE	Derm	Gen Med	Gen Surg	Haem Onc	ICU	Neph/ Renal	Neuro	OB-GYN	Ortho	Other /NR	Over-all
Abscess	7:24		0:3	1:3		6:24	5:46	0:1	1:2		1:1	0:2	2:4	0:1	23:111
Cellulitis	2:21		2:4	0:7		4:17	1:6	0:1	0:1	0:1		0:1	3	0:2	9:64
Infected burn	1	2:36		1:2		1:6	0:4	0:2	0:1						4:52
Infected dermatological conditions	1:3			0:3	2:7	0:4	0:3	0:1						0:1	3:22
Infected sore	2:3		0:1	0:1		3:7	0:4	0:1			0:1		1:3	1:0	7:21
Infected ulcer	4:31	0:1	0:6	7:35	0:1	15:56	4:13		2:4	0:2		0:1	1:5	0:1	33:156
Line infection	1:1		0:1			3:10	1:5	0:2	1:4	0:3	0:1	0:1	0:1	2:0	8:29
Other wound	4:6		1:2	3:3		3:4	0:13		0:1				1:2	1:0	13:31
Other/unknown	3:17	0:1	0:2	3:7	0:1	7:28	5:13	0:6	0:2	0:2	0:3	0:3	1:6	0:3	19:94
Surgical site	2:21		1:11	1:8	0:2	4:26	6:102	0:4	0:15	1:4	1:1	0:12	9:34	0:3	25:243
Traumatic wound infection	4:41	0:1	2:2	7:30		**25:63**	4:36	0:3	1:4	3:2	0:1	0:2	2:14	1:4	49:203
Vascular diabetes related lower extremity infection	1:11		0:1	2:10		4:9	0:10	0:1	0:1				1:1		8:44
(blank)															
Grand Total	31:180	2:39	6:33	25:109	2:11	75:254	26:255	0:22	5:35	4:14	2:8	0:22	18:73	**5:15**	201:1070

Numbers are in the format No. MRSA: No. MSSA; they are in bold wherever the total number of *S. aureus* was >20 and the proportion of MRSA was $\geq$ 25%

Table 4. Percent susceptibility among staphylococci and streptococci

	Ceftaroline CLSI	Ceftaroline BSAC	Cipro-floxacin	Clinda-mycin	Erythro-mycin	Dapto-mycin	Genta-micin	Line-zolid	Peni-cillin	Tetra-cycline	Tige-cycline	Teico-planin	Vanco-mycin
MSSA (1070)	100	100	91.7	(98.3)[b]	86.4	99.9	98.7	100	NT	93.1	99.7	100	99.9
MRSA (201)[a]	94.1	97.6	20.6	(86.3)[b]	38.7	99.5	91.8	100	NT	87.5	99.8	100	100
S. pyogenes (25)	100	100	No bpt	100	100	100	NT	100	100	80	100	100	100
S. agalactiae (39)	100	100	No bpt	(89.7)[b]	89.7	100	NT	100	100	12.8	100	100	100
S. dysgalactiae (98)	100	100	No bpt	(92.6)[b]	66.0	100	NT	100	100	41.8	98.0	100	100

[a] Excludes supplementary MRSA – see Table 7

Table 5. Percent susceptibility among enterococci

	Ceftaroline CLSI	Ceftaroline BSAC	Ampicillin	Daptomycin	Gentamicin[a]	Quinu/dalfo	Linezolid	Tetracycline	Tigecycline	Teicoplanin	Vancomycin
E. faecalis (30)	No bpt	No bpt	100	90% ≤1 mg/l	50	0	100	10.0	100.0	96.7	96.7
E. faecium (16)	No bpt	No bpt	0	All 2-4 mg/L	66.6	50	100	50.0	100.0	50.0	50.0

Abbreviations as in Table 4

a Percentage with only low level intrinsic resistance, MIC ≤128 mg/L

Table 6. Percent susceptibility among gram-negative bacteria isolated

	Ceftaroline CLSI	Ceftaroline BSAC	Ampicillin	Co-amoxiclav	Cipro-floxacin	Cefotaxime	Gentamicin	Ceftazidime
Citrobacter (13)	84.6	84.6	(15.4)	69.2[a]	100	84.6	100	NT
Enterobacter (38)	68.4	68.4	(23.7)	(5.3)	97.3	68.4	92.1	NT
E. coli (125)	89.6	89.6	38.4	73.6	88.0	94.4	91.2	NT
Klebsiella/ Raoultella (34)	82.4	82.4	0	91.2	94.1	85.3	97.1	NT
Indole-positive Proteeae (11)	81.8	81.8	0	36.3[b]	90.9	81.8	90.9	NT
P. mirabilis (34)	94.1	97.1	79.4	97.1	94.1	97.1	94.1	NT
Serratia (14)`	14.3	35.7	0	7.1	92.9	85.7	100	NT
P. aeruginosa (138)	No bpt	No bpt	NT	NT	92.8		98.6	93.5

Abbreviations as in Table 4

a *C. koseri* susceptible; *C. freundii* and *C. braakii* resistant

b *Proteus vulgaris* and *P. penneri* susceptible, *M. morganii* resistant

513 **Table 7.** MIC distributions of ceftaroline for collected SSSI isolates

	MIC (mg/L)																		
	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256	**Total**
MSSA ISO				1	1	5	134	917	12											**1070**
MRSA ISO							1	19	129	47	5									**201**
inc. suppl[a]							1	48	315	159	8									**530**
MSSA MH agar						6	44	1000	20											**1070**
MRSA MH agar								6	64	119	12									**201**
inc. suppl[a]								7	163	336	25									**530**
S. pyogenes	1	24																		**25**
Group B			1	38																**39**
Group C,G		47	51																	**98**
E. faecalis								2	19	4		2	3							**30**
E. faecium												1					1		14	**16**
Citrobacter						5	5	1							1				1	**13**
Enterobacter																				
spp.						2	16	5	3		1		2	1	2	3	1	1	1	**38**
Escherichia coli					4	41	41	14	12	2	1	2	1			1		1	5	**125**

Indole + ve Proteeae	2	4	2	1							1	1				**11**
Klebsiella/ Raoultella		4	16	4	4	1				1				1	3	**34**
Proteus mirabilis	8	18	3	3	1					1						**34**
Serratia spp.				1	4	5	1	2	1							**14**
Acinetobacter spp.					1	1	2	1						1		**6**
P. aeruginosa						1	65	43	17	2	1	3	4		2	**138**

Table excludes all species groups with fewer than five isolates

a Including also the additional 15 MRSA sought per site.

Dark shading: Resistant based on EUCAST breakpoints

Light shading: species with no breakpoints

525 **Table 8.** Characteristics of 45 ceftaroline-resistant Enterobacteriaceae

	ESBL producers (n=15)	AmpC producers (n=16)	Neither (n=14)
E. coli	7		6
Klebsiella / Raoultella spp.	5		1
Enterobacter spp.	3	9	
Citrobacter spp.		2	
P. mirabilis			1
Indole-positive Proteeae		2	
Serratia spp.		3	6
Cefotaxime-susceptible	0	1	13
Ceftazidime-susceptible	1	3	13
Cefepime-susceptible	2	13	14
Ceftaroline MICs (mg/L)[a]	16->256	2->256	1-8
Ceftaroline/clav MICs (mg/L)[a]	0.06-0.25	8->64	0.06-16[b]

526

527 [a] Based on results on IsoSensitest agar

528 [b] Low values are for *E. coli*, where ceftaroline/clavulanate synergy was observed; high values for *Serratia*, often with antagonism of

529 ceftaroline by clavulanate

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531

Table 9. Ratios of MICs by CLSI methodology on Mueller-Hinton agar : MICs by BSAC methodology on IsoSensitest agar for ceftaroline

	No. isolates with indicated MIC ratio							
	0.25	0.5	1	2	4	8	16	32
B,C,G strep	2	2	95	38				
Enterobacteriaceae		15	160	88	5	1		
Enterococci			24	23				
MRSA		1	99	100	1			
MSSA		7	952	110	1			
Others		1	6	4	2			1
P. aeruginosa			6	13	37	47	32	3
S. pyogenes			3	21	1			