

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

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16
17 **Running Heads**

18 SSSI epidemiology and ceftaroline in the UK

19
20 **Keywords**

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

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24 **Background.** Bacterial skin and skin structure infections (SSSIs) are frequent settings for
25 antibiotic use. We surveyed their UK aetiology and pathogen susceptibility, including to
26 ceftaroline. **Materials and Methods.** Consecutive SSSI isolates were collected at 35 UK
27 hospitals, to a maximum of 60/site, together with 15 'supplementary' MRSA/site. Isolates
28 were re-identified and BSAC susceptibility testing performed, with parallel CLSI agar testing
29 for ceftaroline. **Results.** Isolates (n=1908) were collected from 1756 hospitalised patients,
30 predominantly with surgical and traumatic infections, abscesses and infected ulcers and
31 primarily from General Medicine and General Surgery. They included 1271 *Staphylococcus*
32 *aureus* (201 MRSA), 162 β -haemolytic streptococci, 269 Enterobacteriaceae, 138
33 *Pseudomonas aeruginosa* and 37 enterococci. Most (944/1756) patients had monomicrobial
34 MSSA infections. Resistance rates to quinolones, gentamicin and cephalosporins were
35 <20% in Enterobacteriaceae and <10% in *P. aeruginosa*. MRSA rates varied greatly among
36 hospitals and were 2.5-fold higher in General Medicine than General Surgery. At breakpoint,
37 ceftaroline inhibited (i) all MSSA and 97.6% of MRSA, with MICs of 2 mg/L for the few
38 resistant MRSA, (ii) all β -haemolytic streptococci and (iii) 83% of Enterobacteriaceae. High-
39 level ceftaroline resistance in Enterobacteriaceae involved ESBLs and AmpC enzyme.
40 Ceftaroline MICs by CLSI methodology generally equalled those by BSAC or were two-fold
41 higher, but this differential was 4-16-fold for *P. aeruginosa*. **Conclusion.** Irrespective of
42 patient group, SSSIs were dominated by *S. aureus*. Most pathogens were susceptible; but
43 15.8% of *S. aureus* were MRSA, with locally higher prevalence.

44

45 Introduction

46 Skin and skin structure infections (SSSIs, or 'Acute Bacterial Skin and Skin Structure
47 Infections' or ABSSSI in FDA terminology¹) range from trivial to the life threatening. They are
48 important in both hospitals and the community, with categorisation complicated by the fact
49 that hospital acquired (e.g. post-surgical) SSSIs increasingly manifest in the community,
50 following early hospital discharge.² Regulatory agencies divide SSSIs as 'complicated' or
51 'uncomplicated' according to the depth of the structures involved, but routine practice mostly
52 categorised by type (cellulitis, surgical site *etc.*). SSSI aetiology is dominated by
53 *Staphylococcus aureus* but other common isolates include β -haemolytic streptococci,
54 enterococci, Enterobacteriaceae, anaerobes and *Pseudomonas aeruginosa*.³ In a mixed
55 flora, it is often difficult to distinguish pathogens and secondary colonists with confidence.

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

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

72 **Materials and methods**

73 *SSSI survey*

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

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

88

89 *Identification and susceptibility testing*

90 Isolates were re-identified at AMRHAI as follows: *S. aureus* with Chromagar *Staph aureus*
91 (Chromagar, Paris, France) and PCR for *mecA*;⁷ β -haemolytic streptococci by Lancefield
92 typing using Streptococcal Grouping Latex Kits (Pro-Lab Diagnostics, Merseyside, UK);
93 enterococci and gram-negative bacilli by MALDI-ToF mass spectrometry (MALDI Biotyper,
94 Bruker, Coventry, UK). MICs were determined by BSAC agar dilution on IsoSensitest agar
95 (Oxoid-Thermofisher, Basingstoke, UK),⁸ except that Isotonic agar with 50 mg/L Ca^{2+} (Mast
96 Laboratories, Bootle, UK) was used for daptomycin. Results were graded vs. EUCAST
97 breakpoints (<http://www.eucast.org>), which have been adopted by the BSAC.⁹ Ceftaroline
98 MICs additionally were determined by CLSI agar dilution¹⁰ on Mueller Hinton agar (Oxoid).

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

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

108

109 *Typing of S. aureus*

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

114

115 **Results**

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

122

123 *Patient demographics and infection types*

124 The 1756 source patients for the consecutive isolates comprised 918 men and 838 women;
125 35 aged 18-20 years; 131 from 21-30 years; 152 from 31-40 years; 189 from 41-50 years;
126 224 from 51-60 years; 281 from 61-70 years; 327 from 71-80 years; 308 from 81-90 years

127 and 109 aged 91 years or older. Patients with MRSA averaged 5 years older (66.1 years,
128 SD 19.9 years) than those with MSSA (61.4 years, SD 21.7 years). Referring specialities
129 (Table 1) were dominated by General Medicine and General Surgery, each accounting for
130 around one quarter of patients. Accident and Emergency/Admissions Unit, Care of the
131 Elderly, and Orthopaedic Surgery accounted for a further 7.6-15.2% of patients. Only 4.4%
132 of patients were in intensive care. Patients' infection types are summarised in Table 2:
133 46.4% had surgical, traumatic or other wounds, whilst 16% had ulcers or sores and 11.3%
134 had abscess infections. Among smaller groups, 3.8% of patients had infected burns whilst
135 4.4% had diabetes-related lower extremity infections. Swabs were the dominant specimen
136 type, from 1617/1756 (92%) patients; other samples included pus (n= 73), tissue (n=36), fine
137 needle aspirates (n=14) and catheter tips (n=10).

138

139 *Pathogens in relation of hospital site and infection type*

140 *S. aureus* dominated, being present in 72.4% of infections sampled and the sole pathogen in
141 64.7%. It was present in 60-100% of infections in each hospitalisation category and each
142 infection site (Tables 1 and 2); and was the sole pathogen in $\geq 57\%$ infections at each
143 infection site and in all settings except intensive care (47%). Fully 944/1756 (53.8%) of
144 patients had infections solely involving MSSA. MRSA accounted for 15.8% of *S. aureus*, with
145 proportions exceeding 20% in General Medicine, Neurology and Nephrology/Renal patients
146 and among *S. aureus* isolates from infected lines, infected sores and 'other' wounds. No
147 MRSA were recovered from Haematology/Oncology or (unsurprisingly) Obstetrics-
148 Gynaecology patients and proportions were below 10% among *S. aureus* from Burns Units
149 and burn infections, General Surgery and surgical site infection. The MRSA rate among *S.*
150 *aureus* isolates from General Medicine Patients (22.8%) was 2.5x that (9.3%) among
151 General Surgery patients, with this excess substantially reflecting large numbers of MRSA
152 from traumatic wounds and infected ulcers and sores – groups where the MRSA proportion
153 exceeded 20%. There was little major clustering when hospital site and infection type were
154 combined (Table 3), but it is notable that more than half the General Medicine MRSA were

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

163 No other pathogen group besides *S. aureus* was recovered from more than 15% of
164 all patients. Enterobacteriaceae (n=269) included 125 *E. coli*, 38 *Enterobacter* spp., 34
165 *Proteus mirabilis* and 34 *Klebsiella/Raoultella* spp., 14 *Serratia* spp. 13 *Citrobacter* spp. and
166 11 indole-positive Proteaeae, and were recovered from 252 patients (14.4%, with 17 having
167 multiple species). In 179/252 cases (70.1%), Enterobacteriaceae were the sole pathogens;
168 in the remainder they were co-present with other pathogens, predominantly *S. aureus*.
169 Enterobacteriaceae were most frequent in General and Orthopaedic Surgery and Intensive
170 Care Patients, being present in over 20% of surgical site infections, abscesses and (more
171 surprisingly) line infections, but in fewer than 10% of traumatic wound infections, infected
172 ulcers, infected burns and infected dermatological conditions.

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

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

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

189

190 *Antibiotic susceptibility*

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

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

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

236 combination of cefepime susceptibility and clavulanate-independent resistance implied high-
237 level AmpC activity. MICs of ceftaroline for these isolates ranged from 2->256 mg/L with
238 13/16 values ≥ 8 mg/L. The final group of 14 isolates had low-level ceftaroline resistance
239 (MIC 1-16 mg/L) and were susceptible to the other three cephalosporins or had only
240 intermediate resistance, with MICs never exceeding 2 mg/L: six were *E. coli* and six were
241 *Serratia* spp.; ceftaroline MICs for the *E. coli* isolates were reduced by clavulanate to ≤ 0.12
242 mg/L; those for the *Serratia* spp. were raised by clavulanate in many cases, implying AmpC
243 induction. Overall, ceftaroline retained activity vs. 83.3% of Enterobacteriaceae isolates, with
244 over 80% susceptibility except among *Enterobacter* (68.4%) and *Serratia* spp. (35.4%). No
245 Enterobacteriaceae were non-susceptible to cefotaxime but susceptible to ceftaroline.

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

249

250 *Ceftaroline MICs by BSAC vs CLSI methodology*

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

257

258 **Discussion**

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

263 has come from, but depend on the ward for information about the type of infection and (ii)
264 we depended on laboratories' categorisation of organisms as pathogens. The proportion of
265 SSSIs categorised as polymicrobial (12.6%) was lower than found by others – e.g. 41.4% in
266 a 134-hospital, 12,506-patient US survey³ and 22.8% in Phase III trials with ceftaroline.¹⁵
267 This may reflect differing 'norms' in recording secondary organisms, also our exclusion of
268 coagulase-negative staphylococci, which were included as pathogens or co-pathogens in
269 some surveys though not generally in Phase III SSSI data. Despite these caveats, the unit
270 and clinical site analyses presented in Tables 1 and 2 are mutually consistent with similar
271 aetiology across e.g.: (i) surgical site infections and the General and Orthopaedic Surgery
272 groups, and between burn infections and Burns Unit patients.

273 The species distributions, with *S. aureus* dominating in all subsets agrees with that
274 reported by Lipsky *et al.*³ though percentages differ partly because Lipsky *et al.* accepted
275 CoNS as significant, to the extent of including them as the sole pathogens in 18.2% of
276 infections. *S. aureus* was sole pathogen in 54.7% of Lipsky's monomicrobial SSSIs, rising to
277 66.8% if CoNS were discounted, compared with 64.7% here. Proportions of monomicrobial
278 infections with Enterobacteriaceae, streptococci (pooled), *P. aeruginosa* and enterococci
279 were 10.1%, 9.5%, 3.1% and 3.5%, respectively, in Lipsky's series, rising to 12.3%, 11.6%,
280 3.8% and 4.3% once CoNS were disregarded, compared with 10.1%, 4.7%, 5.8, 1.5% here.
281 Another study of 527 patients with healthcare-associated cSSSI,¹⁶ found *S. aureus* in 48.6%,
282 enterococci in 14.6% and *P. aeruginosa* in 10.1%, whilst the SENTRY surveillance found
283 that *S. aureus* accounted for 45.9% of SSSI pathogens and *P. aeruginosa* for 10.8%.¹⁷
284 Recent Phase III antibiotic trials in complicated SSSI/ABSSSI trials^{18,19} again show a similar
285 distribution, with *S. aureus* in more than half the patients and with β -haemolytic streptococci,
286 *P. aeruginosa* and Enterobacteriaceae in 5-20% each versus enterococci in under 5%. The
287 one radically different report is Public Health England's surgical site surveillance for English
288 hospitals 2013-4,²⁰ which indicates a much lower proportion of *S. aureus* (16% or 18.4%, if
289 rebased to exclude CoNS), with Enterobacteriaceae dominant (26%, or 30% if rebased to

290 exclude CoNS). The dominance of Enterobacteriaceae derived from their high proportion
291 (56.7%) in infection following bowel surgery, where only 13.0% of patients had *S. aureus*. *S.*
292 *aureus* remained the major pathogen in the PHE orthopaedic surgery series, present in
293 54.5%-64.3% of monomicrobial infections. The difference between the low rate of *S. aureus*
294 in the PHE bowel surgery series and the high rate in the present General Surgery group
295 (which should heavily represent bowel surgery) remains unexplained.

296 Asides from underscoring the dominance of *S. aureus*, the present analysis
297 importantly shows: (i) that SSSIs in ICUs had a more diverse aetiology than those in other
298 patient groups, with Enterobacteriaceae and *P. aeruginosa* more prevalent; (ii) that
299 Enterobacteriaceae were also prominent in General and Orthopaedic Surgery patients, and
300 in their surgical site infections; (iii) that, more surprisingly, Enterobacteriaceae were
301 prevalent in line infections and (iv) that streptococci, which were mostly B, C, G types, were
302 most prevalent in Emergency and Admissions Unit patients and Care of the Elderly and in
303 cellulitis, whereas Enterobacteriaceae were rare pathogens in Emergency and Admissions
304 Unit SSSI patients and Care of the Elderly. Such data, together with information on MRSA
305 prevalence, point to settings where broad-spectrum therapy may be desirable in the
306 empirical management of SSSIs. Ceftaroline may have a particular potential in mixed SSSIs
307 that involve MRSA together with Enterobacteriaceae, but these are now rare in the UK: only
308 9/201 MRSA were from mixed infections and these largely had 'unknowns' or *P. aeruginosa*
309 as the second isolate, not Enterobacteriaceae.

310 Rates of resistance were low. Fully 944/1756 patients had monomicrobial MSSA
311 infections. Only 15.8% of *S. aureus* isolates were MRSA and among General Surgery
312 patients, the MRSA rate was <10%. This contrasts with a 61% MRSA rate among *S. aureus*
313 from surgical site infections in England in 1997-9²¹ and doubtless reflects the success of
314 subsequent MRSA reduction programmes, which have also seen a >85% reduction in
315 MRSA bacteraemias in England since their 2003/4 peak.^{22,23} Other settings where MRSA
316 rates were below 10% included Burns Units, Obstetrics and Gynaecology and Haematology-

317 Oncology; an ICU MRSA rate of only 12.5% contrasts with 51.2% among SSSI ICU *S.*
318 *aureus* in 2001²⁴. The higher MRSA rate in General Medicine –two and a half times that in
319 General Surgery– was associated with infected ulcers and ‘Other’ traumatic wounds (Table
320 3). The proportion of MRSA was higher particular hospitals, with 5/35 hospitals accounting
321 for 35% of MRSA. Two of these five sites were in Wales, which had risk-based pre-
322 admission MRSA screening during the survey period than universal screening, as then
323 applied in England. Among other common pathogens, streptococci were universally
324 susceptible, except to tetracycline and erythromycin whilst over 90% of Enterobacteriaceae
325 were susceptible to ciprofloxacin and gentamicin and over 80% were susceptible to
326 cephalosporins. Over 90% of *P. aeruginosa* were susceptible to ciprofloxacin, gentamicin
327 and ceftazidime.

328 Fully 97.5% (98.3% with supplementary isolates) of collected MRSA were
329 susceptible to ceftaroline by BSAC methodology, with this proportion falling to 94.0%
330 (95.1%) by CLSI methodology. Typing found little exceptional about the resistant isolates,
331 which almost all belonged to the EMRSA-15/CC22 and EMRSA-16/CC30 lineages that have
332 long dominated among HA-MRSA in the UK.^{3,25} MICs never exceeded 2 mg/L, whereas
333 values of 4 mg/L have been seen for small minorities of isolates in Greece and Germany,
334 with some of these being shown to harbour PBP2’ mutations.^{26,27} Predictably, ceftaroline
335 lacked activity against Enterobacteriaceae that were resistant to cefotaxime and which had
336 profiles indicating ESBLs or derepressed AmpC. Resistance was seen also in a few further
337 Enterobacteriaceae that lacked clear resistance to other cephalosporins; these
338 predominantly comprised *E. coli* with ceftaroline/clavulanate synergy and *Serratia* spp. with
339 ceftaroline MICs of 1 mg/L; the former group is in keeping with the observation that high-
340 level expression of classical TEM enzymes confers low-level protection against ceftaroline,¹⁴
341 the second simply reflects *Serratia* spp. being inherently less susceptible than other
342 Enterobacteriaceae (mode MIC 1 mg/L vs. 0.12-0.25 mg/L for other genera, Table 6), with
343 the tail of the normal distribution thus being cut by the breakpoint.

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

349

350 **Acknowledgements.**

351 We are grateful those who contributed isolates, as follows: Prof I Gould, Aberdeen Royal
352 Infirmary; Mr C Funston, Antrim Area Hospital; Dr E Sim, Barnsley Hospital; Dr M Williams ,
353 Bristol Royal Infirmary; Ms J Ashby, City Hospital Birmingham; Mr P Hitchcock, Colchester
354 Hospital; Mr P Webber, Crawley Hospital; Mr B Wilson, Crosshouse Hospital; Ms G Jones,
355 Derriford Hospital; Prof K Gould, Freeman Hospital; Mr J Lewis, Gloucester Royal Hospital;
356 Mr G Smith, Hereford County Hospital; Ms A Eyre, Hull Royal Infirmary; Dr A Jepson,
357 Imperial College Healthcare NHS Trust; Ms L Clark, John Radcliffe Hospital; Dr A Swann,
358 Leicester Royal Infirmary; Dr A Bentley, Northampton General NHS Trust; Mr S Davies,
359 Northern General Hospital; Mr K Phipps, Queen Elizabeth Gateshead; Dr E Watson,
360 Raigmore hospital; Ms R Hussain, Royal Bolton Hospital; Mr J Rogers, Royal Cornwall
361 Hospital; Ms R Turner, Royal Derby Hospital; Dr S Majumdar, Royal Gwent Hospital; Ms A
362 Whytell, Royal Lancaster Hospital; Dr J Hemming, Salisbury District Hospital; Ms H
363 Humphrey, Southampton General Hospital; Dr K Bowker, Southmead Hospital; Mr M
364 Eydmann, St Barts & The Royal London; Dr J O' Driscoll, Stoke Mandeville Hospital; Dr A
365 Berrington, Sunderland Royal Hospital; Dr M Wootton, University Hospital of Wales; Ms J
366 Tarn, University Hospital of North Tees; Mr P Lewis, Whiston Hospital; Mr D Weston,
367 Wythenshawe Hospital.

368

369 **Funding**

370 We are grateful to AstraZeneca UK for financial support of this study.

371

372 **Transparency declarations**

373 **DML:** Advisory Boards or consultancy: Accelerate, Achaogen, Adenium, Alere, Allecra,
374 Astellas, AstraZeneca, Auspherix, Basilea, Bayer, BioVersys, Cubist, Curetis, Cycle,
375 Discuva, Forest, GSK, Meiji, Pfizer, Roche, Shionogi, Tetrphase, VenatoRx, Wockhardt.
376 lectures. Sponsored lectures: AOP Orphan, Astellas, AstraZeneca, Bruker, Curetis, Merck,
377 Pfizer, Leo. Shareholdings Dechra, GSK, Merck, Perkin Elmer, Pfizer comprising <10% of
378 portfolio value. **Others** No personal interests, but PHE's AMRHAI Reference Unit, which
379 NW heads, has received financial support for conference attendance, lectures, research
380 projects or contracted evaluations from Achaogen, Allecra, Amplex, AstraZeneca, Becton
381 Dickinson, British Society for Antimicrobial Chemotherapy, Cepheid, Check-Points, Cubist,
382 UK Department of Health, Food Standards Agency, Glaxo SmithKline, Henry Stewart Talks,
383 IHMA, Merck, Meiji, Momentum, Nordic, Norgine, Rempex, Rokitan, Smith & Nephew, Trius
384 Therapeutics, VenatoRx, Wockhardt.

385

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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	Overall %
<i>S. aureus</i>	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
<i>S. pyogenes</i>	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
<i>P. aeruginosa</i>	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
<i>S. aureus</i> 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 % <i>S. aureus</i>	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

481

% 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 %
<i>S. aureus</i>	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
<i>S. pyogenes</i>	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
<i>P. aeruginosa</i>	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
<i>S. aureus</i> 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 % <i>S. aureus</i>	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

482

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

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

487

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 (blank)	1:11		0:1	2:10		4:9	0:10	0:1	0:1				1:1		8:44
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

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489

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 $\geq 25\%$

490 **Table 4.** Percent susceptibility among staphylococci and streptococci

491

	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
<i>S. pyogenes</i> (25)	100	100	No bpt	100	100	100	NT	100	100	80	100	100	100
<i>S. agalactiae</i> (39)	100	100	No bpt	(89.7) ^b	89.7	100	NT	100	100	12.8	100	100	100
<i>S. dysgalactiae</i> (98)	100	100	No bpt	(92.6) ^b	66.0	100	NT	100	100	41.8	98.0	100	100

492

493 ^a Excludes supplementary MRSA – see Table 7

494 **Table 5.** Percent susceptibility among enterococci

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	Cefta- roline CLSI	Cefta- roline BSAC	Ampi- cillin	Dapto- mycin	Genta- micin ^a	Quinu/ dalfo	Line- zolid	Tetra- cycline	Tige- cycline	Teico- planin	Vanco- mycin
<i>E. faecalis</i> (30)	No bpt	No bpt	100	90%	50	0	100	10.0	100.0	96.7	96.7
				≤1 mg/l							
<i>E. faecium</i> (16)	No bpt	No bpt	0	All 2-4 mg/L	66.6	50	100	50.0	100.0	50.0	50.0

496

497 Abbreviations as in Table 4

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

499 **Table 6.** Percent susceptibility among gram-negative bacteria isolated

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	Ceftaroline CLSI	Ceftaroline BSAC	Ampicillin	Co-amoxiclav	Cipro- floxacin	Cefotaxime	Gentamicin	Ceftazidime
<i>Citrobacter</i> (13)	84.6	84.6	(15.4)	69.2 ^a	100	84.6	100	NT
<i>Enterobacter</i> (38)	68.4	68.4	(23.7)	(5.3)	97.3	68.4	92.1	NT
<i>E. coli</i> (125)	89.6	89.6	38.4	73.6	88.0	94.4	91.2	NT
<i>Klebsiella/ Raoultella</i> (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
<i>P. mirabilis</i> (34)	94.1	97.1	79.4	97.1	94.1	97.1	94.1	NT
<i>Serratia</i> (14)	14.3	35.7	0	7.1	92.9	85.7	100	NT
<i>P. aeruginosa</i> (138)	No bpt	No bpt	NT	NT	92.8		98.6	93.5

502

503 Abbreviations as in Table 4

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

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

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

	MIC (mg/L)																		Total	
	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
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
<i>S. pyogenes</i>	1	24																		25
Group B			1	38																39
Group C,G		47	51																	98
<i>E. faecalis</i>								2	19	4		2	3							30
<i>E. faecium</i>												1					1		14	16
<i>Citrobacter</i>						5	5	1							1				1	13
<i>Enterobacter</i>																				
spp.						2	16	5	3		1		2	1	2	3	1	1	1	38
<i>Escherichia coli</i>				4	41	41	14	12		2	1	2	1			1		1	5	125

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

	ESBL producers (n=15)	AmpC producers (n=16)	Neither (n=14)
<i>E. coli</i>	7		6
<i>Klebsiella / Raoultella</i> spp.	5		1
<i>Enterobacter</i> spp.	3	9	
<i>Citrobacter</i> spp.		2	
<i>P. mirabilis</i>			1
Indole-positive Proteeae		2	
<i>Serratia</i> 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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532 **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
<i>P. aeruginosa</i>			6	13	37	47	32	3
<i>S. pyogenes</i>			3	21	1			

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