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Comparison of Different Phenotypic Approaches to Screen and Detect mecC-Harboring Methicillin-Resistant Staphylococcus aureus

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1 Comparison of Different Phenotypic Approaches to Screen and Detect *mecC*-Harboring
2 Methicillin-Resistant S*taphylococcus aureus*
3
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18
19 Running Head: Phenotypic Approaches to Detect *mecC* MRSA
20
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26 **Abstract**

27 Similar to *mecA*, *mecC* confers resistance against beta-lactams, leading to the phenotype of a
28 methicillin-resistant *Staphylococcus aureus* (MRSA). However, *mecC*-harboring MRSA pose
29 special difficulties in their detection. The aim of this study was to assess and compare
30 different phenotypic systems for screening, identification, and susceptibility testing of *mecC*-
31 positive MRSA isolates. A well-characterized collection of *mecC*-positive *S. aureus* isolates
32 (n = 111) was used for evaluation. Routinely used approaches were studied to determine their
33 suitability to correctly identify *mecC*-harboring MRSA including three (semi-)automated
34 antimicrobial susceptibility testing (AST) systems and five selective chromogenic agar plates.
35 Additionally, a cefoxitin disk diffusion test and an oxacillin broth microdilution assay were
36 examined. All *mecC*-harboring MRSA isolates were able to grow on all chromogenic MRSA
37 screening plates tested. Detection of these isolates in AST systems based on cefoxitin and/or
38 oxacillin testing yielded overall positive agreement with the *mecC* genotype of 97.3 %
39 (MicroScan WalkAway™, Siemens), 91.9 % (Vitek 2®, bioMérieux), and 64.9 %
40 (Phoenix™, BD). The phenotypic resistance pattern most frequently observed by AST
41 devices was "cefoxitin resistance/oxacillin susceptibility", ranging from 54.1 % (Phoenix)
42 over 83.8 % (Vitek 2) to 92.8 % (WalkAway). The cefoxitin disk diffusion and oxacillin
43 broth microdilution assays categorized 100 % and 61.3 % of isolates to be MRSA,
44 respectively. The chromogenic media tested confirmed their suitability to reliably screen for
45 *mecC*-harboring MRSA. The AST systems showed false-negative results with varying
46 numbers, misidentifying *mecC* MRSA as methicillin susceptible *S. aureus*. This study
47 underlines cefoxitin's status as the superior surrogate *mecC* MRSA marker.

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49 **Introduction**

50 The still worrying occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) in
51 many parts of the world poses a major challenge to health care systems by increasing the
52 burden of disease. Rapid and effective MRSA identification and susceptibility testing is
53 paramount to prevent further dissemination and to adapt antimicrobial treatment. In 2011, a
54 novel PBP2a-encoding *mecA* homologue designated *mecC* (originally $mecA_{LGA251}$) has been
55 reported with homologies on the nucleotide and protein level of only 70 % and 63 %,
56 respectively [1, 2]. Later on, *mecC* has been confirmed as the genetic determinant that
57 confers methicillin resistance in *S. aureus* for those isolates [3]. Farm and wildlife animals
58 have been revealed as reservoirs for *mecC* MRSA [4, 5], and the zoonotic potential of these
59 livestock-associated MRSA has been shown [6, 7, 8].

60 The limited homology of *mecC* to *mecA* and their respective proteins led to major diagnostic
61 challenges in identification and susceptibility testing of *mecC*-harboring MRSA [9]. In
62 addition to obvious but easily resolved difficulties in targeting the divergent *mecC* nucleotide
63 sequence by DNA-based diagnostic tests [10, 11], phenotypic approaches exhibited
64 considerable difficulties due to comparatively low oxacillin MICs [1, 7, 8] which may be
65 caused by differences in the *mecA* and *mecC* promoters [3]. Moreover, low homology
66 between the encoded PBP2a proteins is the reason for the failure of existing PBP2a
67 agglutination tests to detect *mecC*-positive isolates [5, 7, 8]

68 In this study, we compared several routinely applied diagnostic approaches in their capability
69 to identify *mecC*-harboring MRSA from a comprehensive, heterogeneous, and representative
70 collection. In detail, we compared (i) three (semi-)automated susceptibility testing (AST)
71 systems, (ii) five selective chromogenic agar plates (MRSA screening plates), (iii) a cefoxitin
72 disk diffusion test, and (iv) an oxacillin broth microdilution.

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74 **Results**

75

76 **Applicability of AST systems to detect *mecC*-positive isolates**

77 Analyzing resistance towards cefoxitin and oxacillin by AST systems, different susceptibility
78 patterns were observed. For all systems, the most frequently detected pattern was the
79 combination of the categorization "cefoxitin-resistant, but oxacillin-susceptible", ranging
80 from 54.1 % (Phoenix) over 83.8 % (Vitek 2) to 92.8 % (WalkAway) of all tested isolates
81 (Table 1). In the WalkAway system, three isolates (2.7 %) were categorized cefoxitin- and
82 oxacillin-susceptible, whereas in the Vitek 2 and the Phoenix system, 9 isolates (8.1 %) and
83 39 isolates (35.1 %), respectively, were categorized susceptible to both. One isolate was
84 categorized as cefoxitin-susceptible and oxacillin-resistant by the Phoenix system.
85 The MIC_{90} values for oxacillin were ≥2 µg/ml (Phoenix), 2 µg/ml (MicroScan), and 2 µg/ml
86 (Vitek 2). The MIC_{90} values for cefoxitin were >8 µg/ml (Phoenix) and >4 µg/ml
87 (WalkAway); the Vitek 2 detected 91.9 % of isolates as resistant to cefoxitin without
88 reporting an MIC value. Less than 10 % of isolates were tested resistant to both cefoxitin and
89 oxacillin (Phoenix: 9.9 %; MicroScan: 4.5 %; Vitek 2: 8.1 %).

90

91 **Applicability of chromogenic MRSA screening plates for detection of *mecC*-positive**
92 **isolates**

93 The vast majority of isolates showed typical growth on all tested cefoxitin-containing
94 chromogenic MRSA screening plates. Reduced growth, i.e. smaller colonies, but with
95 characteristic MRSA-indicating color, was observed for a small fraction of isolates (Table 2).
96 Oxoid Brilliance™ MRSA 2 plates showed a mixed phenotypic appearance with blue
97 (presumptive for MRSA) and white colonies for all isolates.

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98 Additionally, a subset of nine isolates and positive control *S. aureus* USA 300, tested in
99 triplicate, showed growth on screening plates from four manufacturers using an inoculum of
100 100 µl from of a 10^{-5} dilution of a 0.5 McFarland standard suspension (approximately 100
101 cfu/plate). MRSA Select™ agar plates (Bio-Rad) were not tested in this additional
102 experiment due to supply unavailability.Negative control *S. aureus* ATCC 29213 exhibited
103 no growth on chromogenic agar plates.
104
105 **Applicability of cefoxitin disk diffusion and oxacillin broth microdilution test for**
106 **detection of *mecC*-positive isolates**
107 The cefoxitin disk diffusion test detected *mecC*-encoded methicillin resistance in 111/111
108 isolates, i.e. 100 %. The oxacillin broth microdilution resulted in a categorization of 43
109 susceptible (38.7 %) and 68 resistant (61.3 %) isolates.
110
111
112 **Discussion**
113 The occurrence of *mecC*-harboring MRSA has been described in several European countries
114 in humans, companion animals, and livestock [14]. While the overall prevalence of these
115 isolates seems to be low, it has been suspected that *mecC* prevalence might be underestimated
116 because of its misidentification as methicillin-susceptible *S. aureus* (MSSA) due to its
117 borderline resistant phenotype. Additionally, negative results in MRSA PCR and
118 agglutination assays if only the *mecA* gene, i.e. PBP2a is targeted, hamper *mecC* MRSA
119 detection efforts. Furthermore, it has been shown that the prevalence of *mecC*-positive
120 *S. aureus* isolates increased at least in Denmark and that *mecC* MRSA isolates are also
121 capable to cause infections in humans [4]. A reliable detection of these isolates is important
122 to ensure both an adequate treatment of *mecC* MRSA infections and the use of the same

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123 prevention measures as already established for *mecA* MRSA. This study revealed that all
124 chromogenic media and the cefoxitin disk diffusion test were able to categorize all *mecC*-
125 positive MRSA properly. Additionally, we were able to show for a subset of strains that
126 inocula as low as approximately 100 cfu per plate result in growth on chromogenic media,
127 indicating that a recovery from clinical swab samples with low MRSA loads can likely be
128 achieved. However, these findings are limited because they could mimic the usual clinical
129 specimen as encountered in the laboratory only partially. To varying degrees, all three AST
130 systems displayed limitations in the ability to detect *mecC* MRSA. While the detection rate of
131 WalkAway (97.3 %) was also high, the Vitek 2 (91.9 %) and particularly the Phoenix system
132 (64.9 %) showed considerably lower rates. A study by Cartwright *et al.* showed a detection
133 rate of 88.7 % (n = 62 *mecC* MRSA) for the cefoxitin-resistant/oxacillin-susceptible pattern
134 using the Vitek 2 [15]; similarly, this AST device detected this pattern in 83.8 % of the tested
135 isolates in our study. The oxacillin broth microdilution performed poorly, showing a
136 detection rate of only 61.3 %. This is in accordance with previous studies [16].
137 In conclusion, automated systems may fail to detect *mecC*-encoded methicillin resistance,
138 while all chromogenic screening media displayed colonies presumptive for MRSA growth. In
139 comparison to oxacillin, cefoxitin was confirmed as superior surrogate marker to detect
140 *mecC*-harboring MRSA isolates. Discrepancies between positive screening results based on
141 the use of chromogenic media and categorization as methicillin-susceptible by AST systems
142 should be verified by molecular assays or disk diffusion.
143
144
145 **Material and Methods**
146 A large set of *mecC*-harboring MRSA isolates (n = 111) from human and animal specimens
147 isolated in Germany, the United Kingdom, and Belgium were included in the study. All

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148 isolates were confirmed as *mecC*-positive by PCR [12] and characterized by *spa*-typing
149 (t843, n = 51; t6292, n = 13; t1736, n = 6; t1535, n = 4; t3391, n = 3; t978, t9165, t742, t6902,
150 t6521, t6220, t5930, t1773, t11706, n = 2 each; t9910, t9738, t9280, t9123, t8842, t7914,
151 t7603, t7189, t6300, t524, t13233, t1207, t11702, t11290, t11120 and not typeable, n = 1
152 each). Isolates were of human (n = 80), unknown (n = 24), bovine/bulk milk (n = 4), sheep (n
153 = 2), and environmental (n = 1) origin. No copy isolates were included.
154 Selective chromogenic agar plates (1. Oxoid: Brilliance™ MRSA 2; 2. bioMérieux:
155 chromID® MRSA; 3. BD: BBL™ CHROMagar® MRSA II; 4. Bio-Rad: MRSA Select™; 5.
156 MAST Diagnostica: CHROMagar™ MRSA) were inoculated with a single colony from
157 overnight blood agar plate cultures. To simulate potentially low inocula of clinical specimens,
158 nine isolates with different *spa*-types (t843, t978, t1207, t1535, t1736, t391, t5930, t6292 and
159 t6902) were each adjusted to 0.5 McFarland standard turbidity and serial dilutions with the
160 final dilution factor of 10^5 were prepared. Subsequently, 100 µl of the final dilutions were
161 used to inoculate all chromogenic media (except MRSA Select™ from Bio-Rad due to
162 supply constraints) and blood agar plates for growth control in triplicate. *S. aureus* strains
163 USA300 and ATCC29213 were used as positive and negative controls, respectively. Growth
164 was evaluated after 24 h and 48 h. Automated systems were inoculated from the same plates
165 as chromogenic media. Automated systems for susceptibility testing were used according to
166 the manufacturers' recommendations, i.e. the BD Phoenix™ (Becton Dickinson, Heidelberg,
167 Germany) was executed with the test panel PMIC-72, the Vitek 2® (bioMérieux, Marcy
168 l'Etoile, France) with the test panel AST P580, and the MicroScan WalkAway® 96 plus
169 (Siemens Healthcare Diagnostics, Eschborn, Germany) with the test panel Pos MIC 28.
170 Cefoxitin disk diffusion assays (Cefoxitin discs, 30 µg, bestbion dx, Cologne, Germany) were
171 performed according to EUCAST and using *S. aureus* ATCC 29213 as control. The
172 EUCAST guidelines (version 7.0, valid from 01.01.2017: Inhibition zone of <22 mm,

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173 resistant) and CLSI criteria (M100-S27, Twenty-seventh Edition, January 2017: inhibition
174 zone of ≤21 mm, resistant) were followed in the interpretation of the results.
175 Oxacillin (Sigma-Aldrich, Taufkirchen, Germany) susceptibility was determined by broth
176 microdilution, using a final inoculum of approximately 5×10^5 CFU/ml and *S. aureus*
177 ATCC 29213 as quality control. MICs were interpreted according to EUCAST guidelines
178 (version 7.0, valid from 01.01.2017: MIC >2 µg/ml) and CLSI criteria (M100-S27, Twenty-
179 seventh Edition, January 2017: MIC ≥4 µg/ml).
180

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248 Table 1: Susceptibility pattern testing cefoxitin and oxacillin for *mecC*-positive *S. aureus*

249 isolates (n = 111)

Cefoxitin/oxacillin susceptibility pattern[a]	Number and (% agreement) of isolates tested by[b]		
	Phoenix	MicroScan WalkAway	Vitek 2
R/R	11 (9.9 %)	5 (4.5 %)	9 (8.1 %)
R/S	60 (54.1 %)	103 (92.8 %)	93 (83.8 %)
S/R	1 (0.9 %)	0 (0.0 %)	0 (0.0 %)
Total R[c]	72 (64.9 %)	108 (97.3 %)	102 (91.9 %)
S/S	39 (35.1 %)	3 (2.7 %)	9 (8.1 %)

250

251 [a] R, resistant; S, susceptible;

252 [b] *S. aureus* ATCC 29213 (MSSA) and *S. aureus* ATCC 43300 (MRSA) were used as quality

253 control strains. Both were correctly categorized by all three systems;

254 [c] Positive agreement based on resistance to at least one of the compounds tested (cefoxitin or

255 oxacillin).

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256 Table 2: Growth on selective chromogenic agar media

Chromogenic agar[a]	Number of isolates (n) and (% agreement) with		
	Normal growth[b]	Reduced growth[c]	No growth
Brilliance™ MRSA 2	111 (100 %)	0 (0.0 %)	0 (0.0 %)
chromID® MRSA	111 (100 %)	0 (0.0 %)	0 (0.0 %)
BBL™ CHROMagar® MRSA II	101 (91.0 %)	10 (9.0 %)	0 (0.0 %)
MRSA Select™	105 (94.6 %)	6 (5.4 %)	0 (0.0 %)
CHROMagar™ MRSA	99 (89.2 %)	12 (10.8 %)	0 (0.0 %)

257

258 [a] *S. aureus* ATCC 29213 (MSSA) and *S. aureus* ATCC 43300 (MRSA) were used as quality
259 control strains;

260 [b] According to the respective manufacturer's instructions;

261 [c] Colonies with smaller size, but with color change as indicated for MRSA.

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