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Letter

Risk factors associated with the onset of daptomycin non-susceptibility in Staphylococcus aureus infections in critically ill patients

Matteo Bassetti, Giovanni Villa, Filippo Ansaldi, Daniela De Florentiis, Carlo Tascini, Piergiorgio Cojutti, Elda Righi, Assunta Sartor, Massimo Crapis, Francesco Giuseppe De Rosa, Federico Pea, Francesco Menichetti

Dear Editor,

Daptomycin use is increasing in clinical practice and in intensive care units due to both its concentration-dependent fast bactericidal activity against Gram-positive organisms, including methicillin-resistant Staphylococcus aureus, and high vancomycin minimum inhibitory concentrations (MICs) [1]. Standard recommended doses (4–6 mg/kg/day) are questioned in favor of higher ones (8–10 mg/kg/day), which could provide higher clinical and microbiological cure rates [2], overcome the augmented renal clearance in septic patients [3], and prevent the onset of antimicrobial non-susceptibility [4]. Therapeutic failure due to the emergence of non-susceptible strains is documented in those infections characterized by high inoculum and deep-seated localizations, such as endocarditis or osteomyelitis, or in cases of standard-dose regimens [5]. Furthermore, prior exposure to vancomycin is a recognized risk factor for decreased susceptibility to daptomycin due to induced changes on the bacterial cell wall caused by the glycopeptide [5].

We evaluated the clinical risk factors associated with the onset of daptomycin non-susceptibility (DNS) in critically ill infected patients by retrospectively reviewing medical data collected on patients treated at three large Italian hospitals from January 2010 to September 2014. All infections caused by DNS S. aureus (daptomycin MIC ≥2 mg/L) were included. The control group consisted of patients affected by infections caused by S. aureus strains susceptible to daptomycin and who were treated with daptomycin. Patients in control group was matched 2:1 to the cases according to the following criteria: hospital location (ward), month of admission, and length of hospital stay at the time of matching. All patients who developed infections caused by DNS were receiving daptomycin. Because of the retrospective nature of the research, the requirement for informed consent was waived.

The “VITEK2” system (BioMerieux, Marcy l'Etoile, France) was used for pathogen identification. The Aris Sensititre instrument for incubating and reading susceptibility plates (Trek Diagnostic Systems Inc., Independence, OH) was used according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints, and Etest strips (BioMerieux) were used to confirm antibiotic resistance. Univariate and multiple conditional logistic regression analysis was performed to identify risk factors that were associated with DNS cases (JMP; SAS Institute, Raleigh, NC). Covariates that were significant at 0.10 in the univariate analysis were further evaluated for inclusion in multivariable regression models, using a stepwise algorithm. All tests were two-tailed, and a p < 0.05 was determined to represent statistical significance.

A total of 19 patients were studied and compared with 38 matched controls. Univariate and multivariate analysis results are reported in Table 1.
Table 1. Characteristics and variables associated with daptomycin susceptible and non-susceptible cases (univariate and multivariate analysis)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daptomycin susceptible (n = 38)</th>
<th>Daptomycin non-susceptible (n = 19)</th>
<th>p value</th>
<th>Variables</th>
<th>Chi-square</th>
<th>Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (59–75)</td>
<td>61 (39–71)</td>
<td>0.058</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>20 (51.3)</td>
<td>12 (63.2)</td>
<td>0.417</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>75 (65–80)</td>
<td>78 (68–92)</td>
<td>0.125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson Index score</td>
<td>3 (2–5)</td>
<td>4 (4–5)</td>
<td>0.122</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>6 (15.4)</td>
<td>9 (47.4)</td>
<td>0.023*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization in the previous 3 months before admission</td>
<td>20 (51.3)</td>
<td>15 (79)</td>
<td>0.051</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>20 (51.3)</td>
<td>10 (52.6)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate source control</td>
<td>20 (51.3)</td>
<td>14 (73.7)</td>
<td>0.156</td>
<td></td>
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<tr>
<td>Previous antibiotic treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glycopeptides</td>
<td>4 (10.3)</td>
<td>11 (57.9)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>13 (33.3)</td>
<td>11 (57.9)</td>
<td>0.094</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>3 (7.7)</td>
<td>7 (36.8)</td>
<td>0.01*</td>
<td>Previous treatment with teicoplanin</td>
<td>4.91</td>
<td>7.96</td>
<td>0.027</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2 (5.1)</td>
<td>1 (5.3)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>12 (30.8)</td>
<td>7 (36.8)</td>
<td>0.767</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betalactams</td>
<td>24 (61.5)</td>
<td>11 (57.9)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pathogen</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Methicillin-susceptible Staphylococcus aureus</td>
<td>8 (13.1)</td>
<td>2 (10.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>30 (76.9)</td>
<td>17 (89.5)</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Main infection site</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Bacteraemia (including endocarditis)</td>
<td>16 (41)</td>
<td>12 (63.2)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Univariate analysis | Multivariate analysis
---|---
Variables | Daptomycin susceptible (n = 38) | Daptomycin non-susceptible (n = 19) | p value | Variables | Chi-square | Odds ratio | p value
---|---|---|---|---|---|---|---
Skin and soft tissues | 9 (23.1) | 4 (21.1) | 0.236 |  |  |  | 0.133
Arthritis/osteomyelitis | 2 (5.1) | 0 | 0.395 | Treatment duration with daptomycin (per unit change) | 3.71 | 1.05 | 0.05
Prosthetic joint | 9 (23.1) | 3 (15.8) | 0.356 |  |  |  | 0.567
Other | 3 (7.7) | 0 | 0.039 |  |  |  | 0.838
Daptomycin dose (mg/kg) | 7.8 (6.8–8.4) | 4.6 (3.4–7.7) | <0.001* | Daptomycin dose <6 mg/kg/day | 18.26 | 23.14 | <0.001
Treatment duration with daptomycin (days) | 12 (9–17) | 23 (19–26) | <0.001* |  |  |  | 0.05
Use of therapeutic drug monitoring | 30 (76.9) | 12 (63.2) | 0.351 |  |  |  | 0.06
Daptomycin concentrations (µg/ml) | 43 (32–54.5) | 35 (25–42) | 0.084 |  |  |  | 0.56
30 days mortality | 6 (15.4) | 4 (21.1) | 0.714 |  |  |  | 0.56

Qualitative values are expressed as a number, with the percentage in parenthesis, and quantitative values are expressed as the median with the interquartile range (25° and 75° percentile) in parenthesis, where appropriate.

* Significant at p < 0.05

Multivariate logistic regression analysis showed that a daptomycin dosage of <6 mg/kg, prior exposure to teicoplanin, and daptomycin treatment duration were independently associated with the selection of DNS cases (Table 1). The odds ratios to be a DNS case were >23 and eight in patients who received a dosage of daptomycin of <6 mg/kg and had a prior exposure to teicoplanin, respectively, and increased by 5 % for every day of treatment.

These findings seem to support the assumption that higher doses of daptomycin (>8 mg/kg/day) may guarantee a faster bacterial clearance by maximizing the concentration-dependent bactericidal activity, thus reducing the exposure time of living bacteria to daptomycin and eventually preventing the onset of DNS. However, it should not be overlooked that most patients in both groups had drug exposure adjusted by means of therapeutic drug monitoring (TDM) and that the lower mean dosage administered to the DNS group may be in line with the need to avoid drug overexposure according to the higher rate of chronic renal disease observed in this group (47.4 vs. 15.4 %).

Worryingly, it should be noted that the extensive use of TDM in both groups as a tool to optimize daptomycin exposure in difficult-to-treat S. aureus infections seems to have been unhelpful in preventing the development of DNS strains.
According to our data, prior treatment with teicoplanin represents a risk factor for the development of DNS, implying a common behavior among glycopeptides that sustains DNS. Prior exposure to vancomycin is a recognized risk factor for decreased susceptibility to daptomycin due to induced changes of the bacterial cell wall [5]. Our results also shed light on the potential role of treatment duration in the increase of daptomycin MICs, suggesting that the treatment should be kept as short as possible to avoid this worrying development.

In conclusion, based on the results of our study, although limited by its retrospective nature and its small size, we identified three potential risk factors for DNS development: a standard dose of daptomycin (<6 mg/kg/day), the previous use of teicoplanin, and longer treatment duration.

References


