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LETTER TO THE EDITOR

Impact of therapeutic choices on outcome of osteomyelitis caused by MRSA

Dear editor,

Kang and coll.[1] reported the data from a large prospective cohort of patients with *Staphylococcus aureus* infection. The authors found that Methicillin resistant *S. aureus* (MRSA) accounted for 57.8% of 4949 cases observed and reported a close relationship between an inappropriate antimicrobial therapy and mortality. However, the study was not tailored to find data about the impact of antimicrobial therapy on outcome of bone and joint infection and no data was provided about the efficacy of the newer antibiotics currently employed for the treatment of osteomyelitis sustained by MRSA.

In an observational study, we considered the cases of osteomyelitis referred to our ward during a 3-year period and evaluated the efficacy of the IV agents commonly used in our hospital (linezolid, daptomycin and teicoplanin) for the treatment of osteomyelitis sustained by MRSA.

Osteomyelitis was defined by: (i) persistent bone pain, erythema or tenderness, (ii) positive cultures from bone biopsy, or from soft tissue biopsy, or from swabs obtained from surgical wounds, or from pus aspirated from soft tissue surrounding the infected bone, (iii) radiographic findings, or operative findings suggestive of infection.[2]

The inclusion criteria were: (i) positive cultures for MRSA from 3 specimens obtained by bone or soft tissue biopsy or by swabs from surgical wounds or pus aspirated from surrounding soft tissue[3]; (ii) *S. aureus* susceptibility assessed by E-test; (iii) age $>$ 18 years. The exclusion criteria were: (i) co-infection with HIV; (ii) evidence of metastatic infection or polymicrobic infection; (iii) previous treatment with the investigated drugs.

Study drugs were administered following standardised protocols: teicoplanin 7 mg $\times$ kg of body weight IV once daily or 14 mg $\times$ kg every other day (drug was started daily and switch on the every other day schedule was allowed after 2 weeks of treatment were completed),[4] linezolid 600 mg every 12 h IV during the first 2 weeks, followed by oral or IV administration on physician's judgment, daptomycin 8 mg $\times$ kg of body weight intravenously once daily. The length of each treatment was left to the discretion of the treating physician and the efficacy was evaluated by intention to treat analysis. Cure was defined by clinical, laboratory and radiologic findings.[2]

One-hundred-fifty-six patients with chronic osteomyelitis were observed, 54 (35%) fulfilled inclusion criteria (median age 58 years [interquartile range 25–66], male:female ratio 1.9:1) (Table 1). Forty-two (78%) reported previous unsuccessful antibiotic treatment and 10 (19%) reported to be affected with chronic diseases. Fracture fixators were present in 11 (20%) cases. C reactive protein (CRP) was elevated in all cases, blood leukocytes were above 10000 cells/μL in 20 (37%) cases. Twenty-nine patients received teicoplanin, 13 linezolid, and 12 daptomycin. Median (IQR) length of antibiotic treatment was 16 (14–20) weeks for cases treated with teicoplanin, 12 (8–12) weeks for cases treated with linezolid, and 11 (6–12) weeks for cases treated with daptomycin. Fig. 1 reports the time to normalization of CRP. Median time to CRP normalization was 7 weeks for daptomycin, 8 weeks for linezolid, and 12 weeks for teicoplanin ($X_2 = 14.1$; $p < 0.001$). Moderate or severe side effects were reported in 4 patients, 3 on linezolid treatment (2 cases had optic neuritis, 1 anaemia), and 1 on Daptomycin treatment (transient increase of Creatin-Kinase), drug had to be withdrawn in all cases reporting side effects after linezolid treatment. Cure rate (intention to treat analysis) was 83% for the cases receiving teicoplanin, 77% for those receiving linezolid and 92% for those receiving daptomycin. Three cases with MIC to teicoplanin $\geq$ 4 μg/ml failed.

Osteomyelitis management may be favourably influenced by an efficacious antibiotic treatment. In this study, a high cure rate was obtained with all the drugs investigated, and responders could reduce the time of disability avoiding further surgical procedures and expensive treatments.

Glycopeptides have largely proven their efficacy against MRSA, but their failure rate increases with the MIC for vancomycin.[5] Patients on teicoplanin treatment reported a cure rate comparable to the other drugs investigated, but CRP normalization occurred after longer time and relapses occurred in three cases after teicoplanin was withdrawn, despite the drug had to be administered for a long period.[4,6–8] Of note, our cases with *S. aureus* MIC to teicoplanin close to the higher range of susceptibility had the higher failure rate.

Linezolid may concentrate within the bone and is available in both IV and oral formulations, giving the advantage of balancing the acquisition costs by the reduction of the periods of hospitalization and IV administration of the drug. In our experience, the response rate was 100% for the cases tolerating linezolid, but it was reduced to 77% in the

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Table 1 Main findings, cure rate and approximate cost of the treatment received.

Findings	Teicoplanin (29 cases)	Linezolid (13 cases)	Daptomycin (12 Cases)
Age [yrs, median (IQR)]	59 (25—66)	58 (26—65)	53 (32—64)
% males	65	69	64
Associate conditions[a] (%)	11 (38)	4 (31)	6 (50)
Time to diagnosis [months, median (IQR)]	8 (5—10)	9 (4—9)	9 (8—12)
Cases (%) with previous ineffective antibiotic treatment	23 (79)	10 (77)	9 (75)
Median treatment period (weeks)	16	12	11
Cure rate (%)	83	77	92
Cost for unit (€)	28[b]	55[c]	93[d]
Daily cost (€)[e]	69	110	104
Total acquisition cost for the treatment period (€)[f]	7728	9240	8008

[a] Associate conditions are considered underlying diseases or the presence of fracture fixators.
[b] Vials containing 200 mg of teicoplanin.
[c] Sacs or pills containing 600 mg of linezolid.
[d] Vials containing 500 mg of daptomycin.
[e] Daily cost was calculated assuming a mean body weight of 70 kg.
[f] Total cost was calculated multiplying each drug median treatment period by the daily cost.

intention to treat analysis, because the side effects lead to the drug withdrawal in 3 cases before a complete cure was obtained. Similar concerns about linezolid toxicity were reported by other authors when the drug was administered for long time and linezolid is currently scheduled only for a 28-day treatment period.[9—11]

A number of studies have shown the effectiveness of daptomycin in the treatment of osteomyelitis.[12,13] In our experience, daptomycin provided an elevated cure rate and the reduction of the treatment period, highlighted by faster normalization of PCR and by the absence of relapses occurring after the drug was withdrawn. Moreover, fracture fixators were present in 4 cases on daptomycin treatment and cure was reported in 3 of these cases, probably, because of the drug efficacy on biofilm forming bacteria.[14]

As the acquisition cost is a major problem related to the current IV drugs active against MRSA, we evaluated the approximate drug cost (Table). In this analysis, the higher acquisition cost of linezolid and daptomycin was balanced by the reduction of the treatment period.

In conclusion, antibiotic treatment is a valuable option for osteomyelitis by MRSA. Daptomycin and linezolid have to be considered at least equivalent to teicoplanin for the treatment of MRSA osteomyelitis and the role of each drug has to be evaluated on the basis of many considerations regarding each drug cost, toxicity and acceptability.

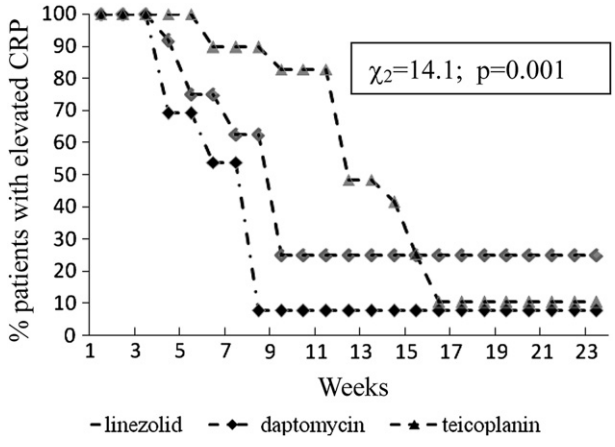

Figure 1 Kaplan—Meier estimate of the time to CRP normalization in relation to treatment.

Ethics

Ethics approval and patient consent/privacy: The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. Patients gave their informed consent to be included in the study.

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Transparency declarations

None to declare.

Conflict of interest

None.

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T. Ascione*
M.D. Iannece
P. Rosario
R. Pempinello
V Division of Infectious Diseases D. Cotugno Hospital, Naples, Italy
E-mail address: tizianascione@hotmail.com (T. Ascione)

P. Pagliano
I Division of Infectious Diseases D. Cotugno Hospital, Naples, Italy

M. Conte
Laboratory of Microbiology D. Cotugno Hospital, Naples, Italy

C. Pempinello
Department of Orthopaedic Surgery S. Gennaro Hospital, Naples, Italy

R. Rotondo
Department of Orthopaedic Surgery CTO Hospital, Naples, Italy

M. Mariconda
Department of Orthopaedic Surgery Federico II University, Naples, Italy

S. Lepore
Department of Orthopaedic Surgery Cardarelli Hospital, Naples, Italy

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* Corresponding author. Via G. Quagliariello 54, Naples, 80131, Italy. Tel.: +39 3397504168; fax: +39 0815908374.