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LETTER TO THE EDITOR

Large discrepancies in linezolid use between French teaching hospitals: A comment on "Antimicrobial stewardship and linezolid"

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Dear Editor,

We read with great interest in a recent issue of the *International Journal of Clinical Pharmacy* the article by Guillard et al. [1]. In this study, they stated that linezolid was used inappropriately in 40 % of cases in their hospital. We would like to discuss their results in light with a recent observational prospective study that we led in two large teaching hospitals: Nantes University Hospital (Hôtel-Dieu and Mother and Children's sites) and Angers University Hospital, during a 6-month period in 2012. Each hospital included intensive care, dermatology, hematology, emergency, infectious disease (ID), pediatric, surgical and gynecology-obstetrics units, allowing comparison to Caen data. All prescriptions of linezolid were included. A data-collection card was created and completed using the patients' medical files, prescriptions collected by the pharmacy and patients' computerized files. Major results are shown in Table 1. Although linezolid use was mostly off-label in each hospital, large discrepancies can be observed. In one hand, at Angers University Hospital, linezolid prescriptions concerned a majority of patients from intensive care unit (46 %). The treatment was mainly prescribed after microbiological documentation (78.6 %) and concerned staphylococci resistant to methicillin in 70 % of cases. On the other hand, at Nantes University Hospital, linezolid was prescribed in majority in medicine units (56 %), with no microbiological data in half of the cases. When these data were available, staphylococci resistant to methicillin was found in 33 % of biological samples.

Concerning ventilator-associated pneumonia (VAP), Wunderink et al. [2] have shown that linezolid was non inferior and statistically superior to vancomycin in end-of-treatment clinical outcome as well as in microbiologic outcome at end of treatment and at end of study. Moreover, it is now well established that linezolid pulmonary diffusion is higher than vancomycin diffusion [3]. At Nantes University hospital, since Zephyr study publication, linezolid was prescribed in first line therapy for VAP. Compared to Nantes retrospective study performed in 2008 [4], this matter of fact could explain the increased prescription of linezolid in this indication (21.4 vs. 16.2 % in 2008). Moreover, de-escalation was systematically initiated after microbiological documentation. This finding underlines the necessity of rapid microbiological results (i.e. MRSA or not). We also observed an empiric use of linezolid at Nantes hematology unit especially for catheter-related infection. In this unit, the ecological environment reveals mostly coagulase-negative staphylococci resistant to methicillin. Therefore, oral route of linezolid presents a real advantage, especially after the removal of a central venous catheter. Linezolid pediatric use has been a special concern at Nantes University Hospital for many years to treat lung diseases or catheter-related infections [4]. Good pulmonary

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Table 1 Comparison of linezolid use in two French University hospitals (main results of a 2012 prospective study) and Guillard et al. study

	Angers	Nantes	Guillard et al. [1]
Study	Prospective study	Prospective study	Retrospective study and prospective interventional study
Year	2012 (6-month)	2012 (6-month)	2009–2013
Hospital description			
Total MSO bed number	1180	1522	1495
Medicine beds	745	868	568
Surgical beds	361	562	359
Total antibiotics DDD (2012)	598.5	436.3	–
Linezolid DDD (2012)	2.38	5.51	3.2
Study demography			
Number of patients	56	153	218
Age mean (years)	62.9	50.6	62
Age range (years)	[11–91]	[9 days–93]	[28–99]
Pediatric patients	1	21	None
Sex ratio (men/women)	1.9	1.89	–
Main hospitalization unit	Intensive care (46.4 %)	Medicine care (56 %)	Intensive care (56 %)
Main comorbidity	Renal failure (28.6 %)	Immune depression (46 %)	–
Off-label use (%)	71.5	61.1	45
Main indications			
Pulmonary infection (%)	23.4	21.4	49
SSTI (%)	5.3	17.5	15
Sepsis (%)	14.3	28.6	5
CR infection (%)	26.8	13.1	–
BJI (%)	9	4.5	7
Abdominal infection (%)	7.1	5.2	7
Others (%)	14.1	9.7	6
Prescription without microbiological data (%)	21.4	49.7	–
MR Staphylococci (%)	70	33.1	–
MRSA	n = 19	n = 15	7 %
MRSE	n = 8	n = 18	7 %
MR-CNS	n = 4	n = 10	–
First place treatment (%)	33.9	36.6	51
Switch for other treatment 3 days after beginning (%)	8.9	31.4	–

MSO medicine, surgery and gynecology-obstetrics, *DDD* defined daily dose per 1000 inhabitants per day, *SSTI* skin and soft tissue infections, *CR* catheter-related, *BJI* bone and joint infection, *MR* methicillin resistant, *MRSA* methicillin resistant *Staphylococcus aureus*, *MRSE* methicillin resistant *Staphylococcus epidermidis*, *MR-CNS* methicillin resistant coagulase negative staphylococci

diffusion and large number of coagulase-negative staphylococci resistant to methicillin isolated from pediatric blood cultures are the main reasons for child prescriptions. Despite a large decrease of linezolid use in bone and joint infection (BJI) treatment between 2008 (22 %) and 2012 (4.5 %), linezolid is preferred to vancomycin in Nantes immediately after BJI surgeries and microbiological results in order to avoid a catheter setting for vancomycin treatment. Finally, there is a concern about optimal dosing strategies for vancomycin to achieve an AUC/MIC ratio $\geq$400 for serious infections [5], since AUCs are not routinely performed and intensive dosing strategies may be associated with increased acute kidney injury rates [6].

Regarding antimicrobial stewardship, linezolid use was strongly controlled in Guillard et al. study by the pharmacy department in first line and then by an ID physician. At Angers University Hospital, linezolid prescriptions were also checked through a systematic call to an ID physician when indication written on the order form was off-label. At Nantes University Hospital, linezolid prescription must be written on an order form too, but off-label indications were not systematically approved by an ID physician following a

pharmacist call. These antimicrobial stewardship differences could also have taken part in discrepancies observed in linezolid use.

In summary, we agree with the conclusion of Guillard et al, that linezolid use must be appropriate in order to slow down the emergence of bacterial resistance. However, in some controlled cases, due to its advantages over vancomycin in terms of PK/PD, linezolid can be prescribed in first line therapy provided that de-escalation is rapidly performed after microbiological results. A strong collaboration between clinicians, microbiologists and pharmacists remains the only way to ensure the proper use of antibiotics.

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