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RESEARCH ARTICLE

Antimicrobial stewardship and linezolid

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Abstract *Background* Since 2002, linezolid, the first representative of the oxazolidinone class, has been widely prescribed, sometimes outside of approved indications. However, several cases of clinical outbreaks due to linezolid-resistant organisms have been reported, and its relatively high cost represents an economic challenge for hospital settings. *Objectives* The aim of this study was to assess the impact of different actions conducted by an antimicrobial stewardship team (AST) to control over-prescription of linezolid with regard to the defined daily dose (DDD) per 1,000 inhabitants per day. *Setting* This work was conducted in a 1,495-bed hospital from 2009 to 2013. An AST, gathering the departments of pharmacy, microbiology, and infectious diseases, assessed the pertinence of linezolid use and associated effect on the prescriber. *Method* A retrospective study was conducted throughout 2009. Three different evaluations were prospectively carried out, each for 3 months, between 2011 and 2013. *Main outcome measure* The indicators chosen to monitor the consumption of linezolid were the DDD per 1,000 inhabitants per day, which enabled a comparison to be made between hospitals from 2004 to 2012, and of the pertinence of its prescription by different departments. *Results* From 2009 to 2013, 239 patients were evaluated through three 3-month stages. Prescriptions were for off-label use in 45 % of cases. Prescriptions were considered appropriate in 60 % of cases. Unsuitable treatment was either modified or discontinued (62 and 38 % of cases, respectively). Mean duration of linezolid treatment was 8 days, i.e. below the national mean duration reported in the literature. To highlight the impact of action taken by the team, a consensual strategy to treat ventilator-acquired pneumonia was elaborated with principal prescribers. Throughout the study, the mean DDD per 1,000 inhabitants per day increased very slowly and was lower than the eleven other French hospitals, which were secondarily included in this study. *Conclusion* The multidisciplinary approach that was adopted for therapeutic education and delivery control led to an improvement in the proper use of linezolid. Similar strategy should be extended to other antimicrobial agents, such as carbapenems, for which both cost and risk of resistance emergence are of major concern.

Keywords Antimicrobial stewardship · Clinical impact · France · Linezolid use · MRSA

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Impact of findings on practice statements

- Prescribers of antimicrobial therapies in hospital should collaborate closer with the departments of pharmacy and microbiology.
- In our hospital linezolid was used inappropriately. There is no reason to believe that this will be different in other hospitals, unless special protocols have been effectuated.

Introduction

Linezolid is the first agent of a new class of antibiotics referred to as oxazolidinones. It was approved by the Food and Drug Administration (FDA) in 2002 for the treatment of hospital- and community-acquired pneumonia and complicated skin and soft-tissue infections, caused by Gram-positive bacteria [1–3]. Linezolid therapy must be prescribed in a hospital setting, after examination by an infectiologist or a microbiologist [4].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of health care-associated infections and severe infections. Few drugs are available for the treatment of MRSA infections; they include vancomycin (the gold standard), teicoplanin, linezolid, daptomycin and, very recently, ceftaroline [5]. Linezolid is a particularly interesting alternative to vancomycin in nosocomial pneumonia due to MRSA isolates [6]. Indeed, linezolid offers good tissue penetration [7, 8], can be administered orally, and can even be used in the case of renal failure [9]. However, linezolid therapy remains relatively expensive with an average daily cost of €126 in France ($169). Finally, its inappropriate use may induce the development of high-level linezolid resistance through several 23S rRNA mutations or acquisition of the plasmid-mediated c*fr* gene. Linezolid-resistant Gram-positive cocci are still relatively rare in vivo, risk factors for selection of resistance including indwelling devices, protracted therapy and underdosage [2, 10, 11]. Taking into account cost, the risk of emergence of resistance and linezolid antimicrobial activities, linezolid prescription should be reserved for the treatment of MRSA infections as an alternative to glycopeptides [11–14].

At the University Hospital in Caen, France, linezolid has been available since 2004. Since its implementation, linezolid purchasing has had a significant budgetary impact, hence alerting the hospital's antimicrobial stewardship team (AST) and Antimicrobial Use Committee (AUC). The mission entrusted to the AST, which includes infectious disease (ID) physicians, microbiologists and pharmacists, is to optimize clinical outcomes, to reduce the emergence of antimicrobial resistance and to reduce health care costs. Therefore, considering the cost and the antimicrobial spectrum of linezolid, several interventions aimed at monitoring current use and favouring proper use of linezolid were implemented in 2009 as part of an AST program. This was reinforced in 2011 by monitoring the indicators used to study the impact of implemented actions.

Aim of the study

The aim of the study was to prospectively study the impact of the different actions deployed by an AST program on linezolid use.

Ethical approval

Because this study evaluated the proper use of antibiotics and used anonymised data extracted from pharmacy records, it did not require ethical approval.

Methods

This work was conducted in a 1,495-bed tertiary care hospital, including 38 % medicine beds, 24 % surgical beds, 7 % gynaecology-obstetrics beds, and 9.5 % paediatric beds. It is worthy of note that the institution included three intensive care units (ICU) for adults, an ID unit, a department of pneumology and a department of dermatology.

The validated indicator chosen to monitor linezolid consumption was the defined daily dose (DDD) per 1,000 inhabitants per day from 2004 to 2012. The DDD/1,000 inhabitants/day calculation method was as follows: [total quantity of consumed linezolid/1.2 g (daily dose)]/1,000 hospitalization days (HD), for patients admitted to the hospital, excluding those exclusively attending treatment sessions or staying <1 day. The DDD/1,000 inhabitants/day enables inter-institution comparison, year by year at national level. The average DDD/1,000 inhabitants/day for the eleven other French hospitals included in the study was calculated and compared with the DDD/1,000 inhabitants/day of linezolid at the Caen University Hospital between 2002 and 2012 [15, 16]. DDD/1,000 inhabitants/day data were collected in response to requests by email.

The validated monitoring indicators chosen by the AUC to evaluate the use of linezolid and the pertinence of its prescription were: prescribing departments, prescribing physician grade (MD or resident), prescription duration, indications ("European Medicines Agency-approved" use or off-label use), reasons for prescription and requested bacteriological documentation [17]. Oral or parenteral formulation were not indicators since they present the same biological availability (100 %) [3].

Firstly, in order to assess linezolid use and based on patient medical files, a 1-year retrospective study was conducted for all patients treated with linezolid between January 1st and December 31st 2009. A case report form (CRF) was completed for each patient.

Secondly, an interventional prospective study was implemented from 2011 to 2013, based on a targeted clinical audit. It allowed the pertinence of prescriptions to be assessed in accordance with recommendations from the AUC. This study was performed over three stages and within each hospital department, as part of an AST program (Fig. 1). Treatment with linezolid during the

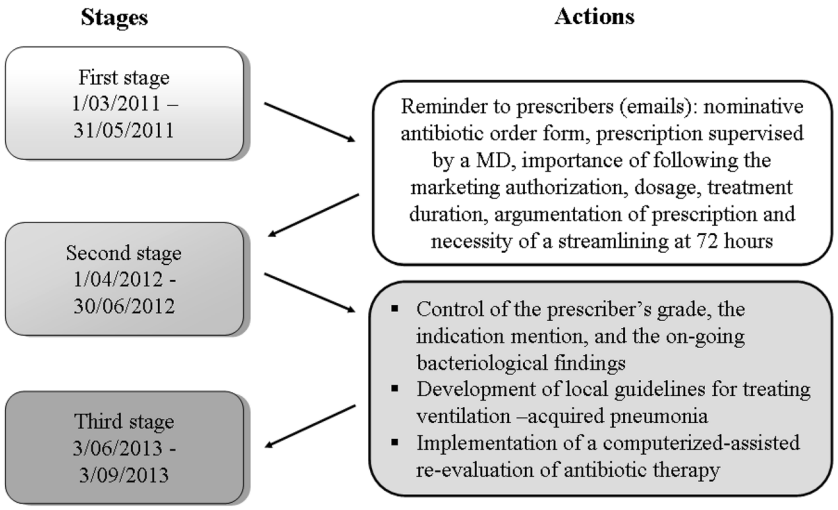

Fig. 1 Method: prospective study

evaluation was the only inclusion criterion. There was no exclusion criterion. For each prescription, a CRF was created and sent by the pharmacy department to the ID unit. A physician (one of three different physicians) from the AST reviewed the prescription with the clinician in charge of the associated patient. The pertinence of the prescription was evaluated and defined according to marketing authorization, publications, clinical experiments and to the patient's history. If unsuitable, treatment was modified or discontinued (Appendix 1). The AUC members met after each stage to define and assess its actions.

Data analysis

Frequencies of off-label use and factors associated with prescription were analyzed between 2009 and 2013 (Chi square test). The mean duration of treatment was compared between 2011 and 2013 (Student's t test for a 95 % confidence interval). A P value <0.05 was considered statistically significant.

Results

From a total of 140 patients treated with linezolid in 2009, 130 were available for this retrospective study (Tables 1 and 2). Linezolid was prescribed in 12 medical departments in the hospital, the ICUs (56 %) in particular. Linezolid was usually prescribed by an MD (28.6 %) or by a resident (33.6 %). In 37.8 % of cases, physicians were unidentified (Table 1). Pneumonia was the most commonly treated condition (Table 2). However, 30 % of prescriptions did not meet marketing authorization criteria. Linezolid therapy was prescribed as first-line treatment in 51 % of cases, either as broad-spectrum antibiotic therapy (28 %) or for infections caused by a Gram-positive pathogen (23 %). It was used as second-line treatment in 49 % of cases. Most patients had received antimicrobial therapy combined with linezolid (66 %): 43 % with piperacillin-tazobactam, 25.6 % with amikacin and 15.1 % with spiramycin. In 15 % of cases, patients had received vancomycin within 15 days prior to linezolid treatment.

We then conducted a clinical practice assessment from 2011 to 2013. During three 3-month stages, of a total of 146 patients treated with linezolid, 109 were included in the prospective study (37 patients were excluded since their CRFs were not fully available). Results are summarized in Tables 1 and 2.

Around 55 % of prescriptions satisfied marketing authorization criteria throughout the study. Thus, 45 % were for off-label use, such as: severe sepsis, other bronchopulmonary infections, device-related infections… (Table 2). Moreover, the study assessed the pertinence of prescriptions according to indications and to prescription-associated criteria, such as: glycopeptide intolerance, renal failure, no central venous catheter… Linezolid prescriptions were appropriate in 60 % of cases. When inappropriate, treatment was modified (62 %) or antibiotic therapy was discontinued (38 %) by an ID physician from the AST.

Mean duration of linezolid treatment was 6.5 days during the first stage (range 1–17 days), 8 days during the second stage (range 1–49 days), and 6 days during the third stage (range 0.5–20 days). There was no significant difference between stage 1 and stage 2 ($P = 0.172$), between stage 2 and stage 3 ($P = 0.117$), or between stage 1 and stage 3 ($P = 0.737$).

There was a significant difference between the indications in 2009 and the indications in 2013 ($P = 0.0156$),

Table 1 Indicators: departments, physicians, mean duration of linezolid treatment

	Retrospective study 2009	Prospective study 2011 First stage	Prospective study 2012 Second stage	Prospective study 2013 Third stage
TOTAL prescriptions	140	43	54	49
TOTAL analyzed prescriptions	130	36	30	43
Study duration (months)	12	3	3	3
No. of prescription by departments (%)				
Surgical ICU	34 (26.1)	6 (16.7)	7 (23.3)	8 (18.6)
Medical ICU	39 (30)	9 (25)	4 (13.3)	5 (11.6)
Cardiovascular surgery	18 (13.8)	3 (8.3)	6 (20)	7 (16.3)
Other surgical departments[†]	10 (7.7)	4 (11.2)	3 (10)	5 (11.7)
Infectious diseases unit	3 (2.3)	2 (5.6)	2 (6.7)	2 (4.7)
Neurology	10 (7.7)	3 (8.3)	0	1 (2.3)
Pneumology	6 (4.6)	3 (8.3)	1 (3.3)	4 (9.3)
Dermatology	0	0	1 (3.3)	1 (2.3)
Other medical departments[‡]	10 (7.5)	6 (16.8)	6 (19.9)	10 (23.3)
Distribution of physician's status (%)				
Hospital practitioner (MD)	37 (28.6)	22 (61)	13 (43.3)	31 (72.1)
Resident	44 (33.6)	14 (39)	13 (43.3)	11 (25.6)
Unidentified	49 (37.8)	0	4 (13.3)	1 (2.3)

ICU intensive care unit

[†] Visceral surgery, orthopaedic surgery and traumatology

[‡] Cardiology, emergency unit, gerontology, haematology, hepatology and gastroenterology, internal medicine, nephrology, otorhinolaryngology, rheumatology, urology

and between prescription-related factors in 2009 and in 2013 ($P < 0.001$) (Table 2).

From 2004—the year linezolid became available in the Caen University Hospital—to 2008, the budget for linezolid purchasing increased approximately twofold every year: 2005: €27,034; 2006: €60,350; 2007: €147,878; 2008: €281,470 (exponential increase: $y = 12518e^{0.7925\times}$ and correlation coefficient $R^2 = 0.9961$). The hospital's DDD/1,000 inhabitants/day increased between 2004 and 2008, with a peak in 2008. The DDD/1,000 inhabitants/day stabilized between 2009 and 2011, increased in 2011 and 2012, but decreased again in 2013. Finally, the DDD/1,000 inhabitants/day of linezolid in the study hospital was below the average DDD/1,000 inhabitants/day collected from eleven other hospitals in France (Fig. 2).

The number of HD was comparable for all hospitals participating in this study (average = 462,389 HD ± 105,601).

Discussion

The lowest DDD/1,000 inhabitants/day observed in Caen University Hospital since 2009 matched with the implementation of these antibiotic prescription evaluations. It increased in 2011 and 2012, but it decreased in 2013 thanks to the following new action:

1. Education and consensus with resuscitation practitioners;
2. Preauthorization required, thus restricted delivery from the pharmacy department;
3. Intervention by the ID physician from the AST who reviewed all inappropriate prescriptions.

The principal linezolid-prescribing departments were the medical department and the surgical ICUs: patients were admitted to these departments in 56 % of cases in 2009. However, the proportion of linezolid prescriptions in ICUs decreased during the prospective study: 41 % in 2011, 37 % in 2012 and 30 % in 2013. In fact this study, the results of which were presented to the AUC, was well accepted by resuscitation physicians. This work allowed the development and approval of a consensual strategy to treat ventilator-acquired pneumonia (VAP). In this protocol, linezolid was an acceptable second-line treatment when vancomycin was unsuitable (absence of central line, intolerance, renal failure) (Appendix 2).

Furthermore, within the hospital, linezolid used required preauthorization as from the first stage: a nominative

Table 2 New Drug authorization (NDA), off-label use, factors associated with prescription

	Retrospective study 2009	Prospective study 2011	Prospective study 2012	Prospective study 2013
NDA (%)	90 (69)	12 (33)	15 (50)	21 (49)
Pneumonia with identified Gram-positive pathogen	51 (56.7)	9 (75)	5 (33.3)	8 (38.1)
Pneumonia with suspected Gram-positive pathogen	22 (24.4)	2 (16.7)	4 (26.7)	5 (23.8)
Complicated skin and skin structure infections (CSSSI)	17 (18.9)	1 (8.3)	6 (40)	8 (38.1)
Off-label use (%)	40 (31)	24 (67)	15 (50)	22 (51)
Endocarditis	4 (10)	0	0	0
Intra-abdominal infections	11 (27.5)	3 (12.5)	1 (6.7)	1 (4.5)
Device-related infections	10 (25)	0	1 (6.7)	3 (13.6)
Febrile neutropaenia	2 (5)	2 (8.3)	1 (6.7)	1 (4.5)
Bone joint infection	11 (27.5)	2 (8.3)	1 (6.7)	1 (4.5)
Sepsis	0	2 (8.3)	3 (20)	6 (27.3)
Bronchopulmonary infections	0	13 (54.2)	6 (40)	4 (18.2)
Meningitis	0	1 (4.2)	0	2 (9.1)
Localized infections	0	1 (4.2)	1 (6.7)	2 (9.1)
Antibiotic prophylaxis	0	0	0	1 (4.5)
Unidentified	2 (5)	0	1 (6.7)	1 (4.5)
Mean duration of linezolid treatment (day)	8.5	6.5	8	6
[Min–Max]	[1–45]	[1–17]	[1–49]	[0.5–20]
Factors associated with prescription (%)				
Glycopeptide intolerance	19 (14.6)	1 (3.5)	2 (6)	3 (7.5)
Renal failure	48 (36.9)	12 (33)	11 (36)	19 (44)
No central venous catheter	6 (4.6)	9 (26)	11 (36)	14 (33.5)
Inapplicable	57 (43.8)	14 (37.5)	6 (20)	7 (15)
Pertinent prescriptions (%)	–	26 (72)	18 (60)	26 (60)
Unsuitable prescriptions	–	10 (28)	12 (40)	17 (40)
Treatment outcome				
Continued	–	19 (53)	15 (50)	18 (42)
Modified	–	10 (28)	10 (34)	15 (35)
Discontinued	–	7 (19)	4 (13)	7 (16)
Inapplicable	–	0	1 (3)	3 (7)

antibiotic order form was mandatory, prescribing residents were supervised by an MD and all prescriptions were justified. After the third stage of the prospective study, prescriptions evaluated by the ID physician were considered appropriate in 60 % of cases. Education by the AUC, which regularly reiterated linezolid prescription recommendations, together with active intervention by the pharmacy department were the keys to controlling over-prescription of linezolid.

De-escalation of empirical antimicrobial therapy on the basis of culture results could more effectively target the causative pathogen, resulting in decreased duration of antibiotic therapy. Moreover, long-term use of linezolid could be associated with bone marrow suppression, peripheral neuropathy, optic neuropathy and lactic acidosis [1, 9]. Systematic re-evaluation of antibiotic therapy at 72 h, associated with the physician's computerized order entry, as implemented in the study hospital, should improve the de-escalation of antimicrobial therapy. Moreover, for unsuitable prescriptions, treatment with linezolid was discontinued by a physician from the AST. Consequently, the mean duration of linezolid treatment was 6 days during the third stage of the prospective study and did not exceed 20 days.

Linezolid was frequently used to treat pneumonia with identified or suspected Gram-positive pathogen. In the study, 50 % of prescriptions did not meet marketing authorization criteria and the proportion of prescriptions

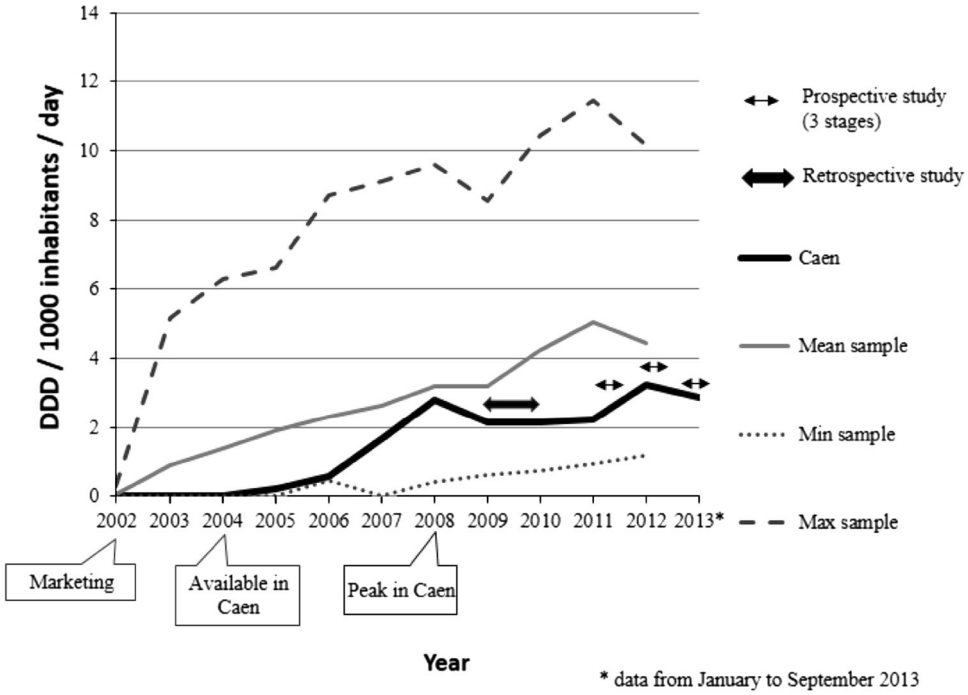

Fig. 2 Defined daily dose (DDD)/1000 inhabitats/day for Caen University Hospital versus mean DDD/1000 inhabitats/day for the other 11 Franch hospitals

considered as unsuitable remains high. In fact, linezolid was effective in several indications: sepsis, endocarditis, intra-abdominal infections, device-related infections and meningitis [1, 9, 10]. However, during the third stage, unjustified prescriptions persisted: unidentified indication (one patient) and pneumonia with resistant pathogen (four patients). To limit these prescriptions, education is a key element, associated with local guidelines for the proper use of linezolid.

It is important to assess which interventions contribute the most towards improving antibiotic use. In the French teaching hospital, the AUC decided to develop an AST program to optimize clinical outcomes, to reduce the emergence of resistance, to limit the occurrence of antibiotic-related adverse effects and to reduce health care costs. To improve the proper use of linezolid, the AST strategy was to implement a prospective and interventional study focusing on the pertinence of prescriptions. This study consisted of three stages. The first stage allowed us to raise awareness of the proper use of linezolid among all prescribers. The second stage was not effective in improving the monitoring of indicators (number of prescriptions, number of unidentified physicians and mean duration of linezolid treatment), whereas the third stage had an impact on these indicators. Consequently, monitoring prescriptions alone resulted in reducing inappropriate use of linezolid but had no long-term beneficial impact. During the third stage, multidisciplinary work, together with the development of a consensual strategy, had an impact on the treatment of VAPs.

In the institution's overall antibiotic budget, the share allocated to linezolid had significantly increased up to 2008. However, the institution's budget was not selected as a monitoring indicator. Its limitations were indeed multiple: variability in costs from 1 year to another, in the number of patients treated with linezolid, and of the budget itself, in addition to the difficulty to compare hospitals. Due to these limitations, we chose the DDD/1,000 inhabitants/day to monitor linezolid consumption. The DDD/1,000 inhabitants/day enabled us to compare exposure to antibiotics with medical activity. Indeed, it allowed us to disregard the bias of price modifications, of daily doses, packaging, etc. and, above all, variations in the number of patients. We assessed exposure to linezolid based on prescription practices and their variations over time. Moreover, the DDD/1,000 inhabitants/day enabled not only the comparison of linezolid consumption from 1 year to another within one hospital, but it also between hospitals. From 2004, the use of linezolid increased in all twelve hospitals in the study, including the Caen University Hospital.

Several studies focusing on monitoring linezolid have been conducted in France to describe the use of linezolid in clinical practice [18–20]. Linezolid was frequently used to treat complicated skin and skin structure infections [18, 19], paediatric infections [18] and conditions beyond

Table 3 Comparison of French studies monitoring linezolid

	Aubin et al. [18]	Megne Wabo et al. [19]	Duhalde et al. [20]	Caen study
Study	Retrospective observational study	Professional Practice Evaluation	Prospective study	Retrospective study and prospective interventional study
Year	2008	2010	2005–2006	2009–2013
Population				
n	179	59	50	218
Age (years)	60	60	62	62
Range	[1–97]	[19–86]	[39–86]	[28–99]
Use				
cSSSI	30 %	24 %	11 %	15 %
Pneumopathy	16 %	15 %	48 %	49 %
Bone joint infection	22 %	–	–	7 %
Septicaemia	–	32 %	–	5 %
Intra-abdominal infection	–	–	13 %	7 %
Paediatric infection	11 %	–	–	0 %
Central catheter infection	–	10 %	–	–
Device-related infection	–	–	13 %	6 %
Pathogen				
MRSA	17 %	22 %	24 %	7 %
MSSA	20 %	7 %	–	16 %
S. epidermidis	29 % MRSE	20 %	34 % MRSE	7 % MRSE
Enterococcus	22 %	15 %	14 %	9 %
Gram-negative pathogen	–	–	–	15 %
no pathogen	–	–	–	15 %
unidentified	12 %	16 %	24 %	5.5 % (data from 2009)
Mean duration of treatment	14 days	11 days	11 days	8 days
[Min–Max]		[1–42]	[1–36]	[0.5–49]

MRSE methicillin-resistant *Staphylococcus epidermidis*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*

marketing authorization criteria. However, there was no validated quantitative indicator such as DDD/1,000 inhabitants/day to evaluate linezolid use in these three different studies. There was only a reference to the mean duration of treatment, which was longer than that in the Caen University Hospital (Table 3).

Finally, as part of an antimicrobial stewardship program, this prospective study involving direct interaction with and feedback to the prescriber resulted in reducing inappropriate use of antimicrobials [20–22]. However, our study design had two weaknesses in that it was performed at only one site and that was retrospective in 2009. The occurrence of adverse effects or drug interactions with serotonergic agents was not evaluated. Furthermore, while the interventions resulted in improvement in the control of linezolid over-prescription, thanks to the discontinuation of unsuitable prescriptions, the study results still reveal the need for improvement. Moreover, evaluations were irregular with 130 analyzed prescriptions in 2009 and 109 between 2011 and 2013. The impact of intervention may vary with time. Action including direct feedback to the prescriber from the ID physician and pharmacy-restricted delivery requiring preauthorization should be widespread to allow long-term assessment. In addition, within the study institution, action taken by the AST should be extended to other antimicrobial treatments: carbapenems or antifungals, which involve greater ecological and economic challenges.

Conclusion

Inappropriate use of linezolid, including its prescription as first-line treatment for infections with suspected Gram-positive pathogens, induces the development of antibiotic

resistance [23]. Currently, there are very few new antibiotics with anti-MRSA activity, such as some oxazolidinones: tedizolid (Phase III trial) and radezolid (Phase II trial) [24, 25]. Therefore, the proper use of linezolid is increasingly important to slow down the emergence of bacterial resistance. The AST is very important in securing the proper use of linezolid, via education and delivery restriction.

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Conflicts of interest The authors declare they have no conflict of interest concerning this article.

Appendix 1: professional practice evaluation: CRF

ASSESSING LINEZOLID PRESCRIPTIONS

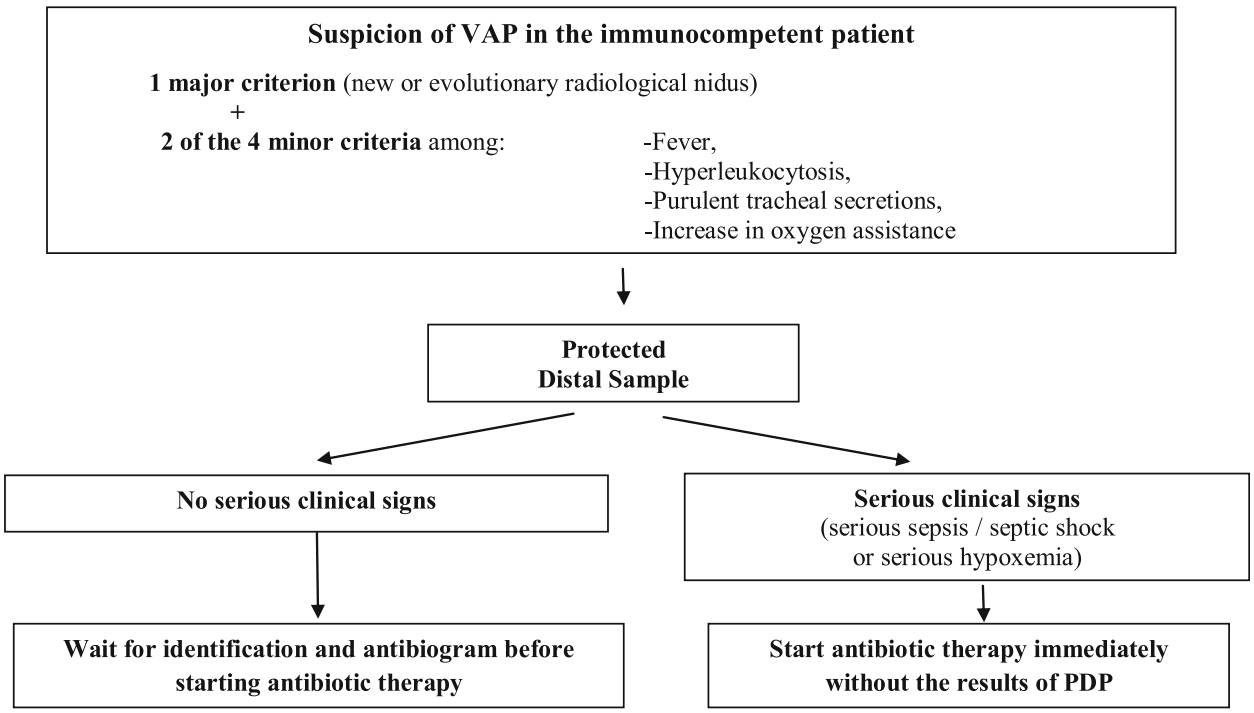
PHARMACY:
UF:
Patient
Date of prescription:
Prescriber title:
Prescriber name:
Administration route: IV ☐ PO ☐

ACTION CONDUCTED BY THE INFECTIOLOGY TRANSVERSAL TEAM (ITT):
Identified clinical infectious disease:
Potential bacteriological documentation:
Other prescribed antibiotics:
Prescriptions according to Market Authorisation (MA) ☐ disregarding MA ☐
Glycopeptide intolerance ☐
Renal failure ☐
No central venous catheter ☐

MEASURES TAKEN BY THE ITT:
Pertinence of the prescription:
☐ Yes
☐ No

SUGGESTION MADE BY THE ITT:
☐ To continue the treatment with linezolid
☐ To replace linezolid, specify with which treatment: .....
☐ Simple interruption of antibiotic therapy

Appendix 2: consensual strategy protocol to treat ventilator-associated pneumonia (VAP)



PROBABILISTIC ANTIBIOTIC THERAPY:

- **If early VAP (≤5 days) and no resistance risk factors*:**

Ceftriaxone (or Levofloxacin IF ALLERGY)

- **If late VAP (>5 days) and/or serious signs and/or presence of resistance risk factors*:**

Piperacillin/tazobactam or Imipenem + Aminoglycosides + Vancomycin**

SYSTEMATICALLY RE-EVALUATE IF THE CULTURE IS POSITIVE TO PROMOTE DE-ESCALATION

Total length of antibiotic therapy is limited to 7 days if satisfactory clinical response except for infections with *P. aeruginosa, Acinetobacter, and Stenotrophomonas* (14 days)

***Antibiotic resistance risk factors**: Antibiotic therapy within the 90 previous days, Hospitalization for at least 5 days or dating back less than 3 months, long-term care, chronic dialyzed patient, previously known presence of SARM, immunodepression or immunosuppressive treatment. Taking into account the hospital department environment.

** Linezolid, which did not show its superiority in terms of mortality, can be an alternative (if creatinine clearance < 30 ml/min).

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