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The intravenous vancomycin prescription practices of French infectious disease specialists: A cross-sectional observational study

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Abstract

Introduction

Vancomycin prescription modalities remain non-consensual. We examined and evaluated the vancomycin prescription habits of infectious disease specialists in France.

Methods

Through an anonymized online questionnaire sent to members of the French Infectious Diseases Society, detailed information on vancomycin prescription modalities was collected.

Results

Out of the 712 physicians contacted, 179 (25%) completed the questionnaire; 174 (97%) of them routinely prescribed intravenous vancomycin: 95 (55%) by continuous infusion only, 12 (7%) by intermittent infusion, while 67 (38%) used the two modalities.

Among continuous administration users, 157 (97%) applied a loading dose of 15 mg/kg or less (n=80, 49%), 20-25 mg/kg (n=33, 20%), or 30 mg/kg or more (n=45, 28%); 143 (88%) used a maintenance dosage of 30 mg/kg/day and 157 (97%) carried out drug monitoring.

Conclusion

In France, infectious disease specialists favor continuous administration of vancomycin using a loading dose, with systematic monitoring of vancomycin serum concentrations.

Highlights

- In France, infectious disease specialists generally prescribe vancomycin by continuous administration, preceded by a loading dose on which there is no consensus, and carry out early monitoring of serum concentrations.
- Evaluation of co-administration of concomitant antimicrobials, dedicated venous access, and choice of a central intravenous catheter for prolonged treatment are not routine.
- Our results suggest an imperative need to improve the modalities of intravenous vancomycin administration.

1. Introduction

Notwithstanding the advent of novel antibiotics active against Gram-positive cocci (GPC), intravenous vancomycin remains the most widely used antibiotic in treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). The pharmacokinetic/pharmacodynamic parameter that best predicts vancomycin *in vivo* activity is the area-under-the-curve over 24 hours to minimum inhibitory concentration (AUC_{0-24}/MIC) ratio ≥ 400 . As this ratio cannot be routinely determined, serum vancomycin concentrations function as surrogate markers [1]. Even though expert groups have proposed guidelines for therapeutic vancomycin monitoring [2,3] uncertainties remain concerning the optimal target of serum vancomycin concentrations. In addition, the optimal dosing strategy (loading and maintenance doses) for rapid production of satisfactory therapeutic concentrations remains a

challenge for physicians. As regards patients in intensive care units (ICUs) with severe *S. aureus* infections, dosing strategies were recently investigated [4,5]; however, little is currently known concerning less severe situations.

The objective of the present study was to describe the vancomycin prescription habits of French infectious disease specialists (IDS).

2. Material and methods

2.1 Study design and population

For this multicentric observational study, all members of the French Infectious Diseases Society (FIDS) were contacted by email and asked to complete a questionnaire, available online for 2 months (September and October 2020), with 4 reminders sent out. The questionnaire was also addressed to members of the Network of Young French Infectious Diseases Specialists (NYFIDS).

2.2 Data collection

The questionnaire comprised 29 questions divided into 3 parts, participants' demographic characteristics; practices regarding vancomycin prescription, whether continuous or intermittent administration; and use or non-use of a loading dose (LD), dosage, dose adjustments, therapeutic vancomycin monitoring and administration modalities.

2.4 Statistical analysis

Data were described using median and interquartile range (IQR) for continuous data, and frequencies and percentages for categorical data.

Analyses were performed first for the overall IDS population, and then

separately according to prescribing habits (continuous versus intermittent infusion). Bivariate analyses were performed to determine the factors associated with LD dosage in continuous administration of intravenous vancomycin, using Fisher's exact test for categorical data. All statistical tests were two-sided, and a p-value < 0.05 was considered significant. Data were analyzed with the R Studio statistical software package, version 6.3.2.

3. Results

Out of 712 SPILF members, 179 (25%) completed the questionnaire; the 5 (3%) physicians who never prescribed intravenous vancomycin were excluded. Among the remaining 174 physicians, 162 (93%) routinely used continuous infusion administration, 95 (55%) of them exclusively; 79 (45%) used intermittent infusion administration, exclusively by 12 (7%); and 67 (38%) used both regimens.

3.1 Demographic characteristics of infectious disease specialists

Participants were primarily senior physicians practicing in public hospitals (*Table 1*). There was no significant demographic difference between continuous or intermittent administration prescribers.

3.2 Continuous infusion administration

A LD was routinely carried out (n=157, 97%) at 15 mg/kg or less by 80 (49%), and at 30 mg/kg or more by 45 (28%). The LD was similar regardless of the situation (infection site, bacteria, severity, hospital ward) for 103 prescribers (64%) (*Table 2*).

Daily maintenance dosage was 30 mg/kg/d in 88% (n=143), the therapeutic target of serum vancomycin was 20-25 mg/L for the

majority (79%; n=128), at least 30 mg/L for 10% (n=16) and less than 15 mg/L for 8% (n=13). Therapeutic drug monitoring was performed before 24 hours after vancomycin initiation in 42% of cases (n=65), between 24 and 48 hours in 18% (n=28), and after 48 hours in 40% (n=63).

All in all, 83 (51%) reported systematic use of dedicated venous access, 59 (36%) considered use of a central venous line for prolonged treatment only, and 16 (10%) checked drug interactions before using the same venous access.

The only difference noted between ICU and non-ICU practitioners was use of a significantly higher LD of 30 mg/kg among the former (56% vs 28% for non-ICU practitioners, p-value 0.03) (*Table 3*).

In bivariate analyses, residents were more likely to administer a high LD, i.e., 30 mg/kg, as compared to senior doctors (55% vs 23%, p-value 0.01), whereas years of experience, qualification and position in a medical unit were not associated with LD dosage (p-values, 0.73, 0.49 and 0.74 respectively) (*Table 3*).

3.3 Intermittent infusion administration

Out of 79 prescribers of intermittent infusion, 34 (43%) routinely favored this mode of administration. The initial dose varied considerably from one prescriber to another, as 48% prescribed a first dose of 15 mg/kg or less and 46% an initial dose of 30 mg/kg or more. All in all, 19% adjusted the initial dose according to the situation. Most prescribers used a daily maintenance dosage of 30 mg/kg/d (n=66; 54%) (*Table 2*). Vancomycin was administered every 12 hours by 58 (74%), every 8 hours by 12 (17%), every 6 hours by 6 (7%), and every 24

hours by 3 (3%). Fifty-two (66%) declared that they never exceeded a unitary dose per injection of 1500-2500 mg, while 18 (33%) sometimes prescribed unitary doses of 3000 mg. All prescribers declared that they monitored vancomycin trough concentrations.

4. Discussion

The main finding on French IDS's vancomycin prescription practices was that continuous administration is the most frequent modality (93% overall), with 55% of practitioners using it exclusively. While continuous infusion has never shown any benefit in terms of mortality [6,7], it nonetheless offers several advantages: firstly, as compared to intermittent regimen, it is associated with decreased nephrotoxicity [8]; secondly, it facilitates monitoring of serum vancomycin levels; and thirdly, it may reduce overall costs [9]. Although IDSA recommendations [2] suggest intermittent administration insofar as Bayesian methods estimate AUC/MIC with two samples, continuous administration estimates AUC with only one sample, and is easier to carry out.

Another finding was a lack of consensus concerning the loading dose suited to initiation of continuous administration. ICU practitioners used a higher LD, in line with pharmacokinetic data justifying its recommendation for patients with septic shock and/or complex MRSA bacteremia [2,10], the reason being that increased volume of distribution necessitates a higher LD in order to obtain target serum concentrations of vancomycin [11]. However, only 28% of practitioners used a LD of 30 mg/kg or more, regardless of the clinical situation

(infection site, bacteria, severity, hospital ward). To our knowledge, no published work has explored the correlation between vancomycin loading dose and target trough concentrations in patients hospitalized in standard medical wards. One study, which was conducted in an emergency department and included patients primarily presenting with skin or lung infections, showed higher serum vancomycin concentrations after a LD of 30 mg/kg (vs 15 mg/kg) at 12 hours via intermittent administration, without investigating clinical or therapeutic outcomes [12]. Conversely, a higher LD is associated with increased risk of nephrotoxicity [13]. Therefore, it is of critical importance to adjust LD dosage according to the clinical situation, and to be cognizant of a risk of cumulative toxicity when applying a high 30 mg/kg LD followed by a 30 mg/kg continuous regimen.

A minority of IDs declared that they routinely screened for drug co-administrations, given the fact that association with other nephrotoxic treatments increases the risk of nephrotoxicity [13]. Moreover, non-dedicated venous access exposes patients to physical incompatibilities such as precipitation, which may lead to sub-therapeutic dosage [14]. If dedicated and/or central venous access is not available, it is recommended to check out drug compatibilities, to observe guidelines concerning dilution and administration speed, to regularly change infusion sites, and to favor intermittent administration for prolonged treatments.

Although therapeutic monitoring of serum vancomycin was systematically performed, the time between vancomycin initiation and monitoring varied greatly among physicians. With a half-life of 4 to 6

hours, steady-state vancomycin serum level is reached after 20-30 hours (i.e., 5 half-lives). Therefore, therapeutic monitoring is recommended just before the 4th injection in cases of intermittent administration and at any time after the 36th hour in cases of continuous administration [2].

Our study has several limitations. First, it only involved SPILF members, and did not provide information on other physicians' prescribing habits. However, and largely through antibiotic stewardship teams (34% of the participants of the present study were working in such teams), a growing number of medical institutions have been following IDS advice and recommendations, the objective being to effectively manage antibiotic prescription. Second, only 25% of FIDS members completed the questionnaire, limiting our interpretations regarding the entire IDS community. That said, the number of respondents was high compared to other studies evaluating vancomycin prescription [15,16]. Third, the aim of this study was not to assess the efficacy or toxicity of the different regimens. Lastly, this was a declarative study, with no control of actual practices. Hence, the data collected may not comprehensively reflect the latter, as physicians may report what they should do, rather than what they really do.

In conclusion, the IDSs having participated in this survey usually prescribe intravenous vancomycin through continuous administration, preceded by a non-consensual LD, with early monitoring of serum concentrations. Co-administration evaluation, a dedicated venous access, and choice of a central intravenous catheter for prolonged treatment are not routine. The integration of clinical pharmacists in

antimicrobial stewardship teams, in line with recent guidelines of the French Ministry of Health (DGS/Mission antibiorésistance/DGOS/PF2/DGCS/SPA/2020/79 of 15 May 2020), could yield needed improvement. Studies evaluating therapeutic serum vancomycin levels, toxicity and efficacy according to LD are necessary in view of determining optimal LD dosage in non-ICU patients.

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Tables

Table 1: Characteristics of infectious disease specialists

	N (%)
	Total=174
Years of experience, years [range]	13 [8 - 21]
Grade	
Resident	23 (13)

Practitioner	135 (78)
Professor	16 (9)
Role	
Antimicrobial stewardship teams	59 (34)
Hospital ward	115 (66)
Intensive care physician	
Yes	16 (9)
No	158 (91)
Training	
Infectious disease specialization	64 (37)
Training course in antibiotic therapy	109 (62)
None	1 (1)
Workplace	
Public hospital	147 (85)
Private hospital	26 (15)
French Region	
Auvergne Rhône Alpes	13 (7)
Bourgogne Franche-Comté	11 (6)
Bretagne	5 (3)
Centre Val de Loire	5 (3)
Corse	2 (1)
Grand Est	17 (10)
Haut de France	15 (9)
Ile de France	39 (22)
Normandie	8 (5)
Nouvelle Aquitaine	17 (10)
Occitanie	17 (10)
Pays de Loire	7 (4)
Provence Alpes Côte d'Azur	11 (6)
Overseas French territories	7 (4)

Table 2: Usual continuous and intermittent vancomycin administration by infectious disease specialists

	Continuous infusion N (%) Total=162	Intermittent infusion N (%) Total=79
Main practice		
Yes	136 (84)	34 (43)
Loading dose		
Yes	157 (97)	79 (100)
Loading/initial dose (mg/kg)		
< 15	1 (1)	1 (1)
15	79 (49)	38 (48)
20-25	33 (21)	4 (5)
≥ 30	45 (29)	36 (46)
Adjustment of loading/initial dose according to:		
Type of infection	12 (7)	5 (6)
Bacteria	1 (1)	0 (0)
Severity of patient	33 (20)	9 (11)
Hospital ward	9 (6)	2 (2)
Daily maintenance dose (mg/kg/d)		
≤ 15	5 (3)	7 (9)
20-25	14 (9)	6 (8)
≥ 30	143 (88)	66 (83)
Therapeutic monitoring		
Yes	157 (97)	79 (100)

Table 3: Bivariate analysis of loading dose in participants using continuous administration, according to physician characteristics (n=157)

	Loading dose (mg/kg)			p-value
	15 N (%) Total=79	20 – 25 N (%) Total=33	≥ 30 N (%) Total=45	
Experience since graduation (years)				0.73
< 10 (n=53)	24 (45)	11 (21)	18 (34)	
]10-14] (n=35)	21 (60)	7 (20)	7 (20)	
≥ 14 (n=69)	34 (49)	15 (21)	20 (29)	
Grade				0.01
Resident (n=20)	7 (35)	2 (10)	11 (55)	
Practitioner (n=122)	63 (52)	31 (25)	28 (23)	
Professor (n=15)	9 (60)	0 (0)	6 (40)	
Role				0.74
Antimicrobial stewardship teams (n=58)	29 (50)	14 (24)	15 (26)	
Hospital ward (n=99)	50 (51)	19 (19)	30 (30)	
Intensivist				0.04
Yes (n=16)	6 (38)	1 (6)	9 (56)	
No (n=141)	73 (52)	32 (23)	36 (25)	
Training				0.49
Infectious disease specialization (n=55)	25 (45)	13 (24)	17 (31)	
Training course in antibiotics (n=102)	54 (53)	20 (20)	28 (27)	
Workplace				0.10
Public hospital (n=132)	71 (54)	27 (20)	34 (26)	
Private hospital (n=24)	8 (35)	5 (22)	11 (43)	

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Authors' contributions

M. Lemaitre: Methodology, Software programming, Formal analysis, Investigation, Writing original draft, Visualization

A. Galy: Conceptualization, Methodology, Investigation, Writing review & editing, Visualization, Supervision, Project administration

V. de Lastours: Writing review & editing, Visualization

P. Thill: Resources, Writing review & editing, Visualization

P. Tattevin: Resources, Writing review & editing, Visualization

A. Lefort: Conceptualization, Methodology, Investigation, Writing review & editing, Visualization, Supervision, Project administration

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