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Abstract

Purpose. In 2011, the French Agency for Safety of Health Products issued guidelines underlining the principles of proper aminoglycosides' use. The aim of the survey was to evaluate adherence to these guidelines two years after their issue.

Methods. Characteristics of patients receiving aminoglycosides were recorded by voluntary facilities during a 3-month survey in 2013-2014. The modalities of aminoglycosides treatment were analysed by comparison with the French guidelines.

Results. 3323 patients were included by 176 facilities. Patients were mainly hospitalized in medical wards (33.0%), and treated for urinary-tract infections (24.7%). Compliance regarding the clinical indication and the daily aminoglycosides dose was observed in 65.2% and 62.9% of the cases, respectively. A 30-minute once-daily IV administration was recorded in 62.5% of the cases. Aminoglycosides treatment duration was appropriate (≤5 days) for 93.6% of the patients. When considering the four criteria together, 23.2% of the patients had a treatment regimen aligned with the guidelines. Requests for measurements of peak and trough AG serum concentrations matched the guidelines in 24.9% and 67.4% of the cases, respectively.

Conclusions. Two years after guidelines issue, aminoglycosides use remains unsatisfactory in French health-care facilities. Efforts should be made for guidelines promotion, especially regarding the issue of underdosing.

Introduction

Despite their rather old age, aminoglycosides (AG) continue to be widely used for the treatment of severe infections, including endocarditis, due to Gram-negative bacilli, staphylococci or enterococci, partly due to their broad antibacterial spectrum and the recent emergence of multi-resistant microorganisms. AG pharmacokinetic and pharmacodynamic properties include rapid concentration-dependent bactericidal activity, and a narrow therapeutic index (renal and auditory toxicity). The therapeutic effect is highest if the peak plasma concentration (Cmax)/minimal inhibiting concentrations (MIC) ratio is over 8 to 10 [1,2]. As most broad-spectrum antibiotics, AG are used in clinical practice on an empirical basis as well as after availability of antibiotic susceptibility tests. In fact, because of their toxicity, AG are recommended only in the first days of treatment, i.e. when the bacterial inoculum is heavy, but also when the causative agent and its antibiotics susceptibility are unknown.

Because of AG characteristics, special attention should be given to AG daily dose determination, treatment duration, route of administration, and in some settings, to drug monitoring.

Although these requirements are known since the mid-1980s, AG use remained often inappropriate, in adult patients [3,4], as well as in the paediatric population [5,6].

In 2011, a multidisciplinary group of experts was commissioned by the French Agency for Safety of Health Products (ANSM) to develop up-to-date recommendations on the proper use of intravenous AG [7]. Two years after their issue, we decided to evaluate the appropriateness of AG prescriptions in the light of these recommendations.

Methods

Study design

Practitioners of public and private heath-care facilities registered to the French society for infectious diseases (SPILF, www.infectiologie.com) or to the French observatory for national epidemiology of bacterial resistance to antibiotics (ONERBA, www.onerba.org) were asked to participate in an observational prospective study on AG use. From November 2013 to January 2014, each facility had to record data for at least 10 consecutive inpatients, or all inpatients if less than 10 cases were eligible, treated by AG. Topical and prophylactic uses of AG were excluded. Only the first prescription was considered in case of multiple AG regimens during the study period.

Data collection

Basic demographic data, renal function, prior history of hospitalization and antibiotic treatment in the previous three months, or received since admission and before the first AG administration were recorded.

Data regarding AG prescription included the site of infection, empirical versus documented treatment, presence of septic shock or others reasons for AG choice, and concomitant antibiotics used. Modalities of AG treatment included mode of administration, dose administered, treatment duration, and drug monitoring by determining serum concentrations. The modalities of treatment were analysed by comparison with the French recommendations for AG use issued in 2011 by the French for Safety of Health Products [7]. Briefly, appropriate administration was defined as AG administered intravenously over 30 min in a once-daily dose or multiple daily doses in case of endocarditis. Duration was considered appropriate if AG-containing treatment was $\leq$ 5 days, excepted in case of endocarditis, bone and joint infections and cystic fibrosis. Appropriate daily dose was defined as 15-30 mg/kg bodyweight for amikacine, 3-8 mg/kg bodyweight for gentamicin and tobramycin, and 4-8

mg/kg bodyweight for netilmicin. In case of septic shock or severe sepsis, the higher upper limits of the ranges were required. Appropriate AG indications were limited to severe infections (septic shock, complicated pyelonephritis, Gram-positive endocarditis, infections due to *P. aeruginosa*, *Acinetobacter sp*. …), high-risk infections (late nosocomial infections and foreign-body infections) or infections in high-risk patients (cystic fibrosis, newborns, and immunosuppressed patients). Monitoring of AG peak serum concentration was not required if treatment duration was ≤ 3 days, except in cases of septic shock, severe burns, febrile neutropenia, intensive care units (ICU) patients with mechanical ventilation, morbid obesity, polytrauma patients, cystic fibrosis. Monitoring of AG trough concentration was required in case of planned or effective treatment duration > 5 days, and in case of severe renal impairment, as declared by clinicians. In other cases, no trough monitoring was required.

Multidrug-resistant bacteria were defined as Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL), or resistant to carbapenems, and methicillin-resistant *Staphylococcus aureus* (MRSA). Enterobacteriaceae resistant to extended-spectrum cephalosporins but susceptible to carbapenems and ESBL-negative, and antibiotic resistance patterns of *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolates were also recorded.

Statistical analysis

Continuous variables are expressed as median and range, and were compared by using the Kruskal-Wallis test. Chi^2 test of Fisher's exact test were used when appropriate for comparing categorical variables. For multi-level categorical variables, chi^2 tests for homogeneity are presented. Statistical analysis was performed by using STATA (STATA Corp, College Station, TX, USA) and $p < 0.05$ was deemed significant.

A multivariate analysis model was developed in order to determine variables independently associated with a daily AG dose in the recommended ranges. Variables with $p < 0.10$ in univariate analysis were introduced in the model, and backward analysis was performed.

Variables not significantly associated with the outcome were removed based on the Wald statistic. The Hosmer-Lemeshov test was used for assessing model' fitness. Only the most parsimonious model, i.e. the model with the least variables and the most significance, is presented.

Results

Facilities

A total of 215 healthcare facilities (25 teaching hospitals, 158 non-teaching or private hospitals and 32 rehabilitation or long-term care facilities) participated in the study. The participating facilities accounted for a total of 56,232 acute-care beds and 21,529 rehabilitation or long-term care beds, representing 19% of all French healthcare beds. Among all facilities, 39 did not record any patient treated by AG during the study period, resulting in 176 facilities that recorded at least one patient treated by AG. Among the 176 latter, 98 (55.7%) declared reviewing systematically all AG-containing regimens, including 79 in all wards of the facility, and 42 by an electronic system. However, only 43 of the 98 (43.9%) facilities reviewing all prescriptions have organized an AG control feedback to the prescribers.

Aminoglycosides use

A total of 3,323 patients with a least one AG regimen were included in the study (Table 1), including 2,007 (60.4%) treated by gentamicin, 1,267 (38.1%) by amikacin, and 49 (1.5%) by another AG (Table 2).

Patients were mainly hospitalized in medical wards (n=1 098, 33.0%), surgical wards (n=1 002, 30.2%), or in ICU (n=600, 18.1%). The median age of the patients was 65.0 (interquartile range IQR, 48-78) years, 20.9% were more than 80 years old, 1,878 (56.5%) were male, and 836 (25.2%) had renal failure (Table 1). Patients were mainly treated for urinary-tract infections (n=822, 24.7%) and digestive or respiratory tract infection (n=653, 19.7% and n=601, 18.1%, respectively).

The use of an AG in the antibiotic regimen was justified by the presence of a septic shock in 447 (13.5%) cases. In the absence of septic shock, AG-containing regimens were prescribed in case of high-risk infections (n=579, 17.4%), infection in high-risk patients (n=292, 8.8%),

and pyelonephritis (n=438, 13.2%). The presence or suspicion of multidrug-resistant organisms accounted for only 129 (3.9%) cases. AG were used on an empirical basis in 2568 (77.3%) cases, and on a bacteriologically documented basis for 755 (22.7%) patients. Among the 755 latter, AG were used to treat infections due to Enterobacteriaceae in 352 (46.6%) patients, *Pseudomonas aeruginosa* in 133 (17.6%) cases, *Staphylococcus aureus* in 148 (19.6%) cases, and streptococci or enterococci in 128 (17.0%) cases.

Administration by a single daily dose was the rule (n=3061, 92.1%), but its duration was over 30 minutes in only 2185 (65.8%) cases. The median daily dose was in the recommended ranges for all AG, although at the lower range, and the median duration was 3 days (IQR, 2-3) days (Table 2).

Compliance

AG compliance with the French guidelines was assessed according to four main criteria.

The **clinical indication** for AG was respected for 2167 (65.2%) patients (Table 3). This proportion was higher for patients treated on a bacteriologically documented basis (75.8%) than for those treated on an empirical basis (62.1%; $p<0.01$). Pyelonephritis and community-acquired digestive tract infections represented 33.2% and 23.0% of inappropriate AG indications, respectively.

Compliance regarding the total daily AG dose was observed for 2091 (62.9%) patients (Table 3). Of interest, patients in large facilities (> 300 beds) or university hospitals were slightly more likely to receive the recommended daily AG dose (65.0%) than in the other facilities (59.6%; $p<0.01$). Patients in facilities claiming having a process for reviewing all AG-containing regimens, including those having an AG control feedback to the prescriber were not more likely to receive the recommended daily AG dose than those in facilities without any AG review process.

Once-daily IV administration over 30 minutes was observed for 2076 (62.5%) patients (Table 3).

The **overall duration of AG** treatment regimen was concordant with the guidelines, i.e. mainly 5 days or less, for 3110 (93.6%) patients. When considering all four criteria together, only 23.2% of the patients had an AG treatment regimen in full accordance with the guidelines. 2.0

In a logistic multivariate analysis, having a normal renal function (Odds ratio, 1.7; 95% confidence interval, 1.3-2.2), and being hospitalised in a large facility (OR: 2.0) were the two variables independently associated with a daily AG dose in the recommended range (Table 4). Others factors, including age ≥ 75 years (OR: 0.7), overweight (OR 0.5), septic shock (OR: 0.07), and infection in high-risk patients (OR: 0.02) were inversely associated to having a dose in the recommended range. All other introduced factors, including MDR bacteria or endocarditis were not independently associated with a dose in the recommended range. When forced in the model although not significant in univariate analysis, none of the variables linked to the review process of AG in the facility were associated with the outcome variable.

Finally, requests for measurements of peak and trough serum concentrations matched the guidelines in 828 (24.9%) and 2241 (67.4%) cases (Table 3).

Discussion

The present survey aimed at evaluating adherence to AG guidelines in French healthcare facilities. The results show that AG are used in all type of wards, and that ICUs represented only 18.1% of all AG prescriptions. As expected, AG were mainly used in association with other antibiotics (97.1%) and on an empirical basis (77.3%). Indications for AG use were considered unnecessary in more than 1 out of 3 cases (34.8%). The total AG daily dose was in the recommended ranges in only 62.9% of the cases. Finally, the AG treatment duration was ≤5 days for a majority of cases (93.6%).

The primary indication of AG use was concordant with the guidelines in 65.2% of the cases. This means that, for one third of the patients, the use of AG could be challenged. Such a result underlines the need for disseminating information regarding AG indications. Of interest, patients with pyelonephritis represented a large part of those with AG use that did not match guidelines criteria. The rise in Enterobacteriaceae producing extended-spectrum beta-lactamase, and in fluoroquinolone resistance in the community may explain AG overuse [8]. After the issue of the French AG guidelines, the French Infectious Diseases Society updated guidelines for the management of community-acquired urinary tract infections (www.infectiologie.com). In the latter, AG are indicated on an empirical basis only in case of complicated pyelonephritis, i.e. with severe sepsis or with need of invasive procedure on the urinary tract. These guidelines should further decrease AG indications in pyelonephritis. On the contrary, AG are part of IDSA guidelines for the treatment of uncomplicated pyelonephritis, but usually as a single antibiotic, which is seldom the case in our study [9].

In the present survey, AG daily dose was in the recommended ranges for 62.9% of the patients. In multivariate analysis, we showed that older age, obesity, septic shock and infections in high-risk patients were factors associated to AG underdosing. Such results have been previously reported [10,11]. This discordance with the guidelines is likely to be partly

linked to the narrow therapeutic index of AG, that encourage prescribers to use lower doses to avoid toxicity, although pharmacokinetic/pharmacodynamic objectives have been described 25 years ago [1,2]. However, AG toxicity is not directly related to peak serum concentration and toxicity remains similar for doses below or within the recommended ranges [12].

Patients with weight > 100 kg are prone to receive AG doses below ranges recommended in the French guidelines. However, it should be noticed that computation of AG daily dose is complex in such patients. Indeed, guidelines are not very clear regarding computation of AG daily dose in overweight or obese patients. The use of the actual body weight, an adaptation of the ideal body weight plus a percentage of the patient's excess bodyweight, or lean weight is still debatable [13–15]. Therefore, efforts should be made to clarify AG dose computation in the overweight population, which may represent more than one third of the patients in many part of the world [16].

Finally, it has been previously reported that ICU patients, and especially those with severe sepsis or septic shock, are at increased risk of AG underdosing, which consequently results in low peak serum concentrations [11,17]. This has been linked to an increase in the volume of distribution per kilogram in these patients. The recent French guidelines have been adapted to take into account the need for increasing AG daily dose in the ICU population. However, our results show that changes have not been taken into account. Despite higher recommended loading doses in the updated guidelines, it has been shown that as much as one third of patients in severe sepsis may have aminoglycosides serum peak level below the therapeutic target [11].

As recommended in French guidelines, more than 93% of the patients received AG for a duration ≤5 days, except for endocarditis and bone and joint infections. The 5-day cut-off is considered as a good compromise between efficacy and safety [18,19]. However, it is currently suggested to use a shorter duration of time, i.e. ≤72 hours of treatment. The

treatment duration could be prolonged to 5 days in case of unsatisfactory clinical improvement or in absence of positive bacteriological result.

Our study has some weaknesses. First it is based on a voluntary participation of facilities, and as always, representativeness could be questioned. However, the large number of patients included in a high number of facilities throughout the French territory may have limited this bias. Second, we did not record any information regarding the initial prescriber of AG-containing regimen, which could have helped to understand discrepancies with guidelines. However, we did not show any differences in overall guideline compliance between facilities with a process for reviewing AG-containing regimens and the others. This raises the question of effective AG stewardship or of facility organisation. Precise data regarding the review process, including the background training of the reviewer or consultant, were not collected.

In conclusion the use of aminoglycosides in French healthcare facilities remains inappropriate in a substantial proportion of cases although guidelines availability since more than two years. This is not surprising when considering the numerous barriers to guidelines implementation. [20] In addition, in France, guidelines diffusion is usually passive or semi-passive, while it has been shown that better antibiotic use requires multifaceted interventions [21,22]. This is especially worrisome regarding the use of an appropriate loading dose. The use of higher loading doses should be widely publicized and use of computerized system for optimized dose computation in coordination with the hospital pharmacist and infectious diseases specialist may help improving this situation.

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Table 1. Characteristics of the 3 323 patients treated by aminoglycosides during the 3-month study period

Continuous variables	**Median**	**Interquartile range**
Age	65	(48-78)
Weight	69	(56-80)
Categorical variables	**N**	**(%)**
Sex male	1 878	(56.5)
Renal insufficiency	836	(25.2)
Recent hospitalization	1 445	(43.5)
Recent antibiotic treatment	899	(27.1)
Ward of hospitalization		
- Medicine	1 098	(33.0)
- Surgery	1 002	(30.2)
- Oncology/haematology	167	(5.0)
- Paediatric	244	(7.3)
- Intensive care unit	600	(18.1)
- Rehabilitation and long-term care units	212	(6.4)
Site of infection		
- Respiratory tract	601	(18.1)
- Digestive tract	653	(19.7)
- Urinary tract	822	(24.7)
- Bone and joints	200	(6.0)
- Endocarditis	126	(3.8)
- Febrile neutropenia	92	(2.8)
- Others	829	(24.9)

Table 2. Characteristics of the 3 323 aminoglycosides treatment regimens

Categorical variables	**N**	**%**
Drug		
- Amikacin	1 267	(38.1)
- Gentamicin	2 007	(60.4)
- Tobramycin	47	(1.4)
Single daily dose	3 061	(92.1)
Intravenous administration over 30 minutes	2 185	(65.8)
AG in combination regimen	3 228	(97.1)
AG in empirical regimen	2 568	(77.3)
Primary indication for AG use		
- Septic shock	447	(13.5)
- Infection in high-risk patient	292	(8.8)
- High-risk infection (late nosocomial infection, foreign body)	579	(17.4)
- Multidrug-resistant organism (confirmed or suspected)	129	(3.9)
- *Pseudomonas* sp. or *Acinetobacter* sp. (confirmed or suspected)	189	(5.7)
- Pyelonephritis	438	(13.2)
- Community-onset digestive tract infection	284	(8.5)
- Endocarditis (confirmed or suspected)	130	(3.9)
- Positive blood culture	97	(2.9)
- Others	738	(22.2)
Continuous variables	**Median**	**Interquartile range**
Daily dose (mg/kg bodyweight)		
- Amikacin	15.4	(13.6-20.5)
- Gentamicin	3.3	(2.8-4.9)
- Tobramycin	5.2	(3.1-6.6)
AG treatment duration (days)	3	(2-3)

485 Table 3. Compliance with aminoglycosides guidelines

Criteria for compliance	**N**	**%**
Indication: treatment of severe infections or of high-risk patients	2 167	(65.2)
Daily dose in mg/kg bodyweight in the recommended range and at the upper limit in case of shock or severe sepsis	2 091	(62.9)
Once-daily intravenous administration over 30 minutes	2 076	(62.5)
Duration ≤ 5 days excepted for endocarditis, bone and joint infections, and cystic fibrosis	3 110	(93.6)
All four criteria above	771	(23.2)
Monitoring of aminoglycoside peak serum concentration	828	(24.9)
Monitoring of aminoglycoside trough serum concentration	2 241	(67.4)

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Table 4. Univariate and multivariate analysis for association with daily aminoglycoside dose in the recommended ranges

Variable	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Large facility	1.2	1.1-1.5	2.0	1.4-2.9
Age ≥ 75 years	0.6	0.56-0.74	0.7	0.56-0.87
Weight ≥ 100 kg	0.7	0.54-0.99	0.5	0.36-0.81
Normal renal function	2.2	1.9-2.5	1.7	1.3-2.2
Primary indication for AG use (confirmed or suspected)				
- Septic shock	0.1	0.08-0.13	0.07	0.05-0.10
- *Pseudomonas* sp. or *Acinetobacter* sp.	2.3	1.5-3.4	-	
- Multidrug-resistant organism	1.8	1.2-2.8	-	
- Infection in high-risk patient	0.05	0.03-0.07	0.02	0.01-0.04
- Endocarditis	2.3	1.5-3.5	-	

OR: odds ratio; CI: confidence interval