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1 **Application of guidelines for aminoglycosides use**

2 **in French hospitals in 2013-2014**

3  
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20  
21 Running title: Aminoglycosides use in French hospitals

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35 **Abstract**

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

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

42 **Results.** 3323 patients were included by 176 facilities. Patients were mainly hospitalized in  
43 medical wards (33.0%), and treated for urinary-tract infections (24.7%). Compliance  
44 regarding the clinical indication and the daily aminoglycosides dose was observed in 65.2%  
45 and 62.9% of the cases, respectively. A 30-minute once-daily IV administration was recorded  
46 in 62.5% of the cases. Aminoglycosides treatment duration was appropriate ( $\leq 5$  days) for  
47 93.6% of the patients. When considering the four criteria together, 23.2% of the patients had a  
48 treatment regimen aligned with the guidelines. Requests for measurements of peak and trough  
49 AG serum concentrations matched the guidelines in 24.9% and 67.4% of the cases,  
50 respectively.

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

54

55 **Introduction**

56 Despite their rather old age, aminoglycosides (AG) continue to be widely used for the  
57 treatment of severe infections, including endocarditis, due to Gram-negative bacilli,  
58 staphylococci or enterococci, partly due to their broad antibacterial spectrum and the recent  
59 emergence of multi-resistant microorganisms. AG pharmacokinetic and pharmacodynamic  
60 properties include rapid concentration-dependent bactericidal activity, and a narrow  
61 therapeutic index (renal and auditory toxicity). The therapeutic effect is highest if the peak  
62 plasma concentration (C<sub>max</sub>)/minimal inhibiting concentrations (MIC) ratio is over 8 to 10  
63 [1,2]. As most broad-spectrum antibiotics, AG are used in clinical practice on an empirical  
64 basis as well as after availability of antibiotic susceptibility tests. In fact, because of their  
65 toxicity, AG are recommended only in the first days of treatment, i.e. when the bacterial  
66 inoculum is heavy, but also when the causative agent and its antibiotics susceptibility are  
67 unknown.

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

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

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

77

78

79

80 **Methods**

81

82 Study design

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

91

92 Data collection

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

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

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

118

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

124

## 125 Statistical analysis

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

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

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

138

139

## 140 **Results**

### 141 Facilities

142 A total of 215 healthcare facilities (25 teaching hospitals, 158 non-teaching or private  
143 hospitals and 32 rehabilitation or long-term care facilities) participated in the study. The  
144 participating facilities accounted for a total of 56,232 acute-care beds and 21,529  
145 rehabilitation or long-term care beds, representing 19% of all French healthcare beds. Among  
146 all facilities, 39 did not record any patient treated by AG during the study period, resulting in  
147 176 facilities that recorded at least one patient treated by AG. Among the 176 latter, 98  
148 (55.7%) declared reviewing systematically all AG-containing regimens, including 79 in all  
149 wards of the facility, and 42 by an electronic system. However, only 43 of the 98 (43.9%)  
150 facilities reviewing all prescriptions have organized an AG control feedback to the  
151 prescribers.

152

### 153 Aminoglycosides use

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

157 Patients were mainly hospitalized in medical wards (n=1 098, 33.0%), surgical wards  
158 (n=1 002, 30.2%), or in ICU (n=600, 18.1%). The median age of the patients was 65.0  
159 (interquartile range IQR, 48-78) years, 20.9% were more than 80 years old, 1,878 (56.5%)  
160 were male, and 836 (25.2%) had renal failure (Table 1). Patients were mainly treated for  
161 urinary-tract infections (n=822, 24.7%) and digestive or respiratory tract infection (n=653,  
162 19.7% and n=601, 18.1%, respectively).

163 The use of an AG in the antibiotic regimen was justified by the presence of a septic shock in  
164 447 (13.5%) cases. In the absence of septic shock, AG-containing regimens were prescribed  
165 in case of high-risk infections (n=579, 17.4%), infection in high-risk patients (n=292, 8.8%),



166 and pyelonephritis (n=438, 13.2%). The presence or suspicion of multidrug-resistant  
167 organisms accounted for only 129 (3.9%) cases. AG were used on an empirical basis in 2568  
168 (77.3%) cases, and on a bacteriologically documented basis for 755 (22.7%) patients. Among  
169 the 755 latter, AG were used to treat infections due to Enterobacteriaceae in 352 (46.6%)  
170 patients, *Pseudomonas aeruginosa* in 133 (17.6%) cases, *Staphylococcus aureus* in 148  
171 (19.6%) cases, and streptococci or enterococci in 128 (17.0%) cases.

172 Administration by a single daily dose was the rule (n=3061, 92.1%), but its duration was over  
173 30 minutes in only 2185 (65.8%) cases. The median daily dose was in the recommended  
174 ranges for all AG, although at the lower range, and the median duration was 3 days (IQR, 2-3)  
175 days (Table 2).

176

### 177 Compliance

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

179       The **clinical indication** for AG was respected for 2167 (65.2%) patients (Table 3).  
180 This proportion was higher for patients treated on a bacteriologically documented basis  
181 (75.8%) than for those treated on an empirical basis (62.1%; p<0.01). Pyelonephritis and  
182 community-acquired digestive tract infections represented 33.2% and 23.0% of inappropriate  
183 AG indications, respectively.

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

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

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

197           In a logistic multivariate analysis, having a normal renal function (Odds ratio, 1.7;  
198 95% confidence interval, 1.3-2.2), and being hospitalised in a large facility (OR: 2.0) were the  
199 two variables independently associated with a daily AG dose in the recommended range  
200 (Table 4). Others factors, including age  $\geq$  75 years (OR: 0.7), overweight (OR 0.5), septic  
201 shock (OR: 0.07), and infection in high-risk patients (OR: 0.02) were inversely associated to  
202 having a dose in the recommended range. All other introduced factors, including MDR  
203 bacteria or endocarditis were not independently associated with a dose in the recommended  
204 range. When forced in the model although not significant in univariate analysis, none of the  
205 variables linked to the review process of AG in the facility were associated with the outcome  
206 variable.

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

209

## 210 **Discussion**

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

218

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

232

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

237 linked to the narrow therapeutic index of AG, that encourage prescribers to use lower doses to  
238 avoid toxicity, although pharmacokinetic/pharmacodynamic objectives have been described  
239 25 years ago [1,2]. However, AG toxicity is not directly related to peak serum concentration  
240 and toxicity remains similar for doses below or within the recommended ranges [12].  
241 Patients with weight > 100 kg are prone to receive AG doses below ranges recommended in  
242 the French guidelines. However, it should be noticed that computation of AG daily dose is  
243 complex in such patients. Indeed, guidelines are not very clear regarding computation of AG  
244 daily dose in overweight or obese patients. The use of the actual body weight, an adaptation  
245 of the ideal body weight plus a percentage of the patient's excess bodyweight, or lean weight  
246 is still debatable [13–15]. Therefore, efforts should be made to clarify AG dose computation  
247 in the overweight population, which may represent more than one third of the patients in  
248 many part of the world [16].  
249 Finally, it has been previously reported that ICU patients, and especially those with severe  
250 sepsis or septic shock, are at increased risk of AG underdosing, which consequently results in  
251 low peak serum concentrations [11,17]. This has been linked to an increase in the volume of  
252 distribution per kilogram in these patients. The recent French guidelines have been adapted to  
253 take into account the need for increasing AG daily dose in the ICU population. However, our  
254 results show that changes have not been taken into account. Despite higher recommended  
255 loading doses in the updated guidelines, it has been shown that as much as one third of  
256 patients in severe sepsis may have aminoglycosides serum peak level below the therapeutic  
257 target [11].

258

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

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

265

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

275

276 In conclusion the use of aminoglycosides in French healthcare facilities remains inappropriate  
277 in a substantial proportion of cases although guidelines availability since more than two years.  
278 This is not surprising when considering the numerous barriers to guidelines implementation.  
279 [20] In addition, in France, guidelines diffusion is usually passive or semi-passive, while it  
280 has been shown that better antibiotic use requires multifaceted interventions [21,22]. This is  
281 especially worrisome regarding the use of an appropriate loading dose. The use of higher  
282 loading doses should be widely publicized and use of computerized system for optimized  
283 dose computation in coordination with the hospital pharmacist and infectious diseases  
284 specialist may help improving this situation.

285

286

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

<b>Continuous variables</b>	<b>Median</b>	<b>Interquartile range</b>
Age	65	(48-78)
Weight	69	(56-80)
<b>Categorical variables</b>	<b>N</b>	<b>(%)</b>
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)

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482 Table 2. Characteristics of the 3 323 aminoglycosides treatment regimens

<b>Categorical variables</b>	<b>N</b>	<b>%</b>
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)
- <i>Pseudomonas</i> sp. or <i>Acinetobacter</i> 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)
<b>Continuous variables</b>	<b>Median</b>	<b>Interquartile range</b>
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)

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484

485 Table 3. Compliance with aminoglycosides guidelines

<b>Criteria for compliance</b>	<b>N</b>	<b>%</b>
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 $\leq$ 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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490 Table 4. Univariate and multivariate analysis for association with daily aminoglycoside dose  
 491 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 $\geq$ 75 years	0.6	0.56-0.74	0.7	0.56-0.87
Weight $\geq$ 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
- <i>Pseudomonas</i> sp. or <i>Acinetobacter</i> 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	-	

492 OR: odds ratio; CI: confidence interval

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