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► **To cite this version:**

jerome robert, Y. Péan, S. Alfandari, J-P Bru, J.P. Bedos, et al.. Application of guidelines for aminoglycosides use in French hospitals in 2013–2014. *European Journal of Clinical Microbiology and Infectious Diseases*, 2017, 36 (7), pp.1083-1090. 10.1007/s10096-016-2892-5 . hal-01560010

HAL Id: hal-01560010

<https://hal.sorbonne-universite.fr/hal-01560010>

Submitted on 11 Jul 2017

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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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30 Word count: 2539

31
32 Key words: aminoglycosides, amikacine, gentamicin, dosage

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 (≤ 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_{max})/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) or to the French observatory for national
85 epidemiology of bacterial resistance to antibiotics (ONERBA, 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 ≤ 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 ≤ 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 β -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. Chi² test of Fisher's exact test were used when appropriate for comparing
128 categorical variables. For multi-level categorical variables, chi² 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 ≤ 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). 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 ≤ 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. ≤ 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

287 **Acknowledgements**

288 In memoriam: Sandrine CLEMENT (www.neanima.fr). Our deepest sympathies go out to her
289 family.

290

291 The Surveillance de la Prescription des Antibiotiques (SPA) group: name (facility, city)

292

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398

399 ***Funding:*** The Société de Pathologie Infectieuse de Langue Française (SPILF) provided

400 financial support for data management.

401

402 ***Competing interests:*** none declared.

403

404 ***Ethical approval:*** not required

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

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482 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)
- <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)
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)

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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 \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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