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Aminoglycoside inhalational therapy: a potential pitfall of antimicrobial stewardship in outpatient settings

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Sir,

Outpatient parenteral antibiotic therapy (OPAT) has become widespread globally.[1] Therefore, surveillance of parenteral antibiotics (PABs) is required in not only inpatients but also outpatients for antimicrobial stewardship programmes (ASP). A nationwide insurance claims database study in Japan indicated that antimicrobial use (AMU) of PABs among outpatients accounted for 13.9% of the total AMU of PABs in 2013. Further, this proportion varied by age group: 29.5% for those <15 years of age; 25.5% for those 15–64 years of age; and 10.2% for those >64 years of age.[2] However, this study did not analyse the detailed usage. To reveal the epidemiology of AMU of PABs among outpatients, we conducted a retrospective observational study using a nationwide insurance claims database in 2016.

The days of therapy (DOTs) of systemic antimicrobial prescription in 2016 were analysed using the National Database (NDB) of Health Insurance Claims and Specific Health Checkups of Japan, from the Ministry of Health, Labor and Welfare in Japan. The antimicrobials were classified according to the anatomical therapeutic chemical (ATC) classification, using the ATC third level.[3] The DOTs were standardized by a population and described as per 1000 inhabitant days (DOTID). The population data were collected from a survey report published by the Ministry of Internal Affairs and Communications in Japan.[4] The epidemiology of AMU of PABs among the outpatients was also analysed among the following three groups: (i) <15 years of age (children); (ii) 15–64 years of age (productive age); and (iii) >64 years of age (elderly).

The AMU of total PABs was 1.60 DOTID and that in outpatients was 0.51 DOTID (31.8%). The most prescribed PABs in inpatients were cephalosporins and carbapenems (0.67 DOTID, 61.6%), followed by penicillins (0.28 DOTID, 25.5%), while the most prescribed PABs in outpatients were aminoglycosides (0.25 DOTID, 49.0%), followed by cephalosporins and carbapenems (0.15 DOTID, 30.0%). The AMU of PABs in outpatients among the three groups (children, productive age and elderly) was 0.77, 0.37 and 0.71 DOTID, respectively. The AMU of aminoglycosides of all PABs among the outpatients in these three groups was 0.56 DOTID (73.3%), 0.17 DOTID (47.2%) and 0.28 DOTID (39.2%), respectively (Figure 1). More than half of all aminoglycosides (55.6%) among the outpatients were prescribed to children and only 15.6% of cephalosporins and carbapenems were prescribed to children.

Our study revealed that the AMU of aminoglycosides in outpatients (0.25 DOTID) was comparable to that of penicillin in inpatients (0.28 DOTID) and 55.6% of the aminoglycosides were administered to children among the outpatients. In Europe, the proportion of aminoglycoside use among all antibiotics for OPAT ranges from high (30%−50%) in Luxembourg, Czech Republic, Norway and Russia to none in Hungary and Iceland.[5] Although aminoglycosides are listed in the OPAT guideline of IDSA, this guideline also warns about the adverse events, such as nephrotoxicity or ototoxity.[6] Thus, generally we do not use aminoglycosides as frequently as β-lactam antibiotics. If aminoglycosides were frequently used for resistant bacterial infections, such as those due to ESBL-producing Enterobacteriaceae, use in the elderly should have been higher than in children. Therefore, frequent prescriptions of aminoglycoside injection in children who are outpatients is counterintuitive. Based on some evidence, we hypothesized that a high proportion of aminoglycoside use in outpatients, especially in children, was associated with inhalational use of parenteral agents

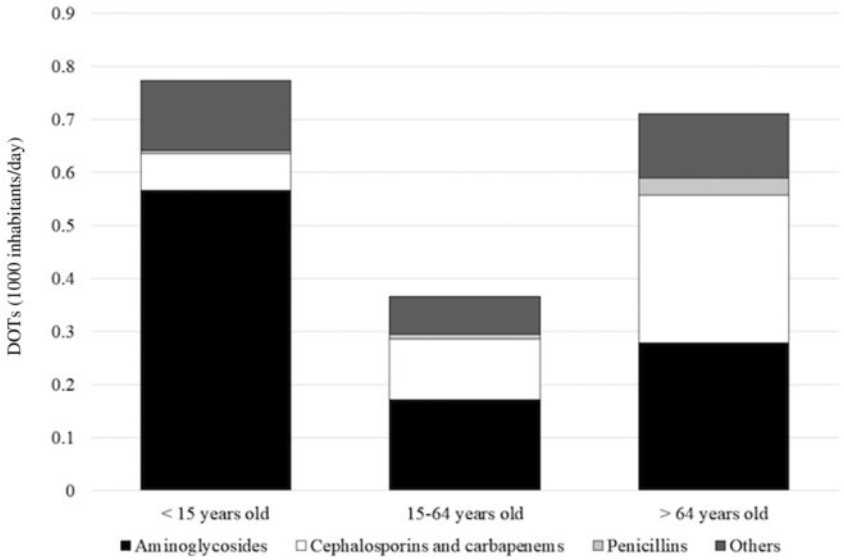

Figure 1. Distribution of the DOTs of PAB among the outpatients in 2016 according to the ATC 3 level by three age groupsAQ6.

in off-label use in Japan. First, the UK Government reported a 58.8% reduction in domestic AMU of aminoglycosides from 2013 to 2017, which was related to a reduction in the inhalational use of aminoglycosides.[7] Second, a previous Japanese case report mentioned that aminoglycosides were traditionally used in inhalational therapy for respiratory infections.[8] Third, OPAT for cystic fibrosis patients is considered to be very low in Japan, because the incidence of cystic fibrosis in Japan (1/350 000) is much lower than in European countries (from 1/2250 to 1/10 500).[9,10] Fourth, the annual incidence of respiratory infection among children was higher than that in the other age groups.[11] These may explain a high proportion of aminoglycosides as inhalational use of parenteral agents among outpatients, especially in children. Generally, aminoglycoside inhalation is not recommended, except for cystic fibrosis patients,[12] and hence its indiscriminate use should be regulated. Aminoglycosides may be frequently used as inhalational therapy in countries where an unexplained high proportion of parenteral aminoglycosides are used among outpatients. Therefore, aminoglycoside use among outpatients needs detailed investigation.

Our study has several limitations. First, claim data do not include the administration route (parenteral or inhalational) of drugs and indications for aminoglycosides. Therefore, a more detailed investigation is required to evaluate the appropriateness of aminoglycoside use among outpatients. Second, although DDD is a more common unit to compare AMU, we have used DOTs in this study. Given that antibiotics are commonly used as single doses per day in OPAT, we believe that DOTs is a better metric to compare outpatient AMU of PABs than DDDs.

In conclusion, our study revealed that aminoglycosides were the most frequently prescribed PABs in outpatient settings, especially in children, in Japan. It was hypothesized that aminoglycosides were used as inhalational therapy. Thus, aminoglycoside inhalational therapy may be a pitfall of ASPs in outpatient settings and further studies evaluating the reasons behind aminoglycoside use in outpatient settings are needed.

Ethics

This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval number: NCGM-G-002505-00).

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Transparency declarations

None to declare.

Supplementary data

The Reviewer report is available as Supplementary data at *JAC-AMR* Online.

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