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

Yoshiki Kusama 1,2, Masahiro Ishikane 1,3*, Chika Tanaka1, Yuki Kimura1, Daisuke Yamasaki4, Masaki Tanabe4, Yuichi Muraki5 and Norio Ohmagari1–3

1AMR Clinical Reference Center, Disease Control and Prevention Center, National Centre for Global Health and Medicine, 1-21-1, Toyama, Shinhu-ku, Tokyo 162-8655, Japan; 2Collaborative Chairs Emerging and Reemerging Infectious Diseases, National Center for Global Health and Medicine, Graduate School of Medicine, Tohoku University, 1-1, Seirya-machi, Aobaku, Sendai-shi, Miyagi 980-8574, Japan; 3Infection Control and Prevention Center, National Centre for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan; 4Department of Infection Control and Prevention, Mie University Hospital, 1577, Kurimamachiya-cho, Tsu-shi, Mie 514-8507, Japan; 5Department of Clinical Pharmacoepidemiology, Kyoto Pharmaceutical University, 5, Misasaginakauchi-cho, Kyoto-shi, Kyoto 607-8414, Japan

*Corresponding author. E-mail: ishikanemasahiro@gmail.com

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 ototoxicity.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.
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. Second, a previous Japanese case report mentioned that aminoglycosides were traditionally used in inhalational therapy for respiratory infections. 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). Fourth, the annual incidence of respiratory infection among children was higher than that in the other age groups. 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, 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).

**Acknowledgements**

The main data from this study were presented at the European Congress of Clinical Microbiology & Infectious Diseases 2019, Amsterdam, The Netherlands (Abstract number: 2846).

We thank all the staff of the AMR Clinical Reference Center in Japan for their support in establishing the National Action Plan on AMR 2016–20 in Japan.

**Funding**

This work was supported by the Ministry of Health, Labor and Welfare (MHLW) research grant of Japan (H29-shinkouyousei-shitei-005).

**Transparency declarations**

None to declare.

**Supplementary data**

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

**References**

1. Lane MA, Marschall J, Beekmann SE et al. Outpatient parenteral antimicrobial therapy (OPAT) practices among adult infectious disease physicians. *Infect Control Hosp Epidemiol* 2014; 35: 839–44.

2. Yamasaki D, Tanabe M, Muraki Y et al. The first report of Japanese antimicrobial use measured by national database based on health
insurance claims data (2011-2013): comparison with sales data, and trend analysis stratified by antimicrobial category and age group. *Infection* 2018; **46**: 207–14.

3 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. 2019. https://www.whocc.no/atc_ddd_index/.

4 Ministry of Internal Affairs and Communications. Portal Site of Official Statistics of Japan - e-Stat. https://www.e-stat.go.jp/en.

5 Coenen S, Muller A, Adriaenssens N et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient parenteral antibiotic treatment in Europe. *J Antimicrob Chemother* 2009; **64**: 200–5.

6 Norris AH, Shrestha NK, Allison GM et al. 2018 Infectious Diseases Society of America Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy. *Clin Infect Dis* 2019; **68**: e1–35.

7 PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report. https://improvement.nhs.uk/resources/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur/.

8 Shirai T, Sato A, Kinoshita Y et al. A case of bronchial asthma induced by inhalation of dibekacin sulfate. *Arerugi* 1994; **43**: 1277–9.

9 Yamashiro Y, Shimizu T, Oguchi S et al. The estimated incidence of cystic fibrosis in Japan. *J Pediatr Gastroenterol Nutr* 1997; **24**: 544–7.

10 Southern KW, Munck A, Pollitt R et al. A survey of newborn screening for cystic fibrosis in Europe. *J Cyst Fibros* 2007; **6**: 57–65.

11 Heikkinen T, Järvinen A. The common cold. *Lancet* 2003; **361**: 51–9.

12 Klepser ME. Role of nebulized antibiotics for the treatment of respiratory infections. *Curr Opin Infect Dis* 2004; **17**: 109–12.