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CASE SERIES

Recurrent/Refractory Multidrug- and Pre-Multidrug-Resistant *Pseudomonas aeruginosa* Infection Cases Maintained by Long-Term, Low-Dose Macrolide Administration

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Abstract: Multidrug-resistant *Pseudomonas aeruginosa* (MDRP) is usually induced by inappropriate use of broad-spectrum antibiotics, and pre-multidrug-resistant *Pseudomonas aeruginosa* (pre-MDRP) is defined as resistance to any two of three antibiotics, such as carbapenems, fluoroquinolones, and aminoglycosides. Two cases of infections with such organisms are reported. Case 1 was a 78-year-old man with esophageal cancer who had pneumonia, treated by meropenem (MEPM) for two weeks because *P. aeruginosa*, which showed good susceptibility to most antibiotics, was isolated. He improved, but his inflammation status and chest X-ray findings worsened on day 21. MDRP was isolated, and he was treated using tazobactam/ceftolozane (TAZ/CTLZ) for 10 days. After improvement, clarithromycin (CAM) 200 mg once per day was then started as long-term, low-dose macrolide therapy. His condition has remained stable for more than six months. Case 2 was a 5-year-old girl with congenital heart abnormalities. She had pneumonia due to *P. aeruginosa* that showed good susceptibility to antibiotics and was treated by MEPM for 10 days. However, MDRP was isolated, and then ciprofloxacin (CPFX), to which MDRP showed good susceptibility, with only intermediate susceptibility to levofloxacin (LVFX), was started. Ten days later, her pneumonia improved, and half-dose (5 mg/kg) CAM three times per day was started as long-term, low-dose macrolide therapy. Her condition has remained stable for more than six months. These two cases, one adult MDRP infection and one pediatric pre-MDRP infection, that were maintained by long-term, half-dose macrolide administration, which might have affected pathogen colonization and host immunomodulation, are presented.

Keywords: azithromycin, clarithromycin, erythromycin, antimicrobial stewardship, *Pseudomonas aeruginosa*

Introduction

Pseudomonas aeruginosa is a representative pathogen that often causes severe pneumonia in hospitalized patients and is susceptible to only a limited number of antibiotic agents.[1,2] Therefore, infections caused by this organism are difficult to cure, often inducing organisms that are resistant to antibiotics, including multidrug-resistant *P. aeruginosa* (MDRP).[3,4] In Japan, MDRP is usually defined as *P. aeruginosa* resistant to carbapenems, fluoroquinolones, and amikacin by the Japan Nosocomial Infections Surveillance (JANIS), a program of the Ministry of Health, Labour and Welfare, and pre-MDRP has been defined as resistant to two of the three above antibiotics.[5] The increasing resistance of *P. aeruginosa* is a growing threat to the clinical management of such infections, and pre-MDRP has often appeared when antibiotics were used inappropriately.[6] Therefore, isolation of pre-MDRP means an intermediate resistance state, and its recognition is relevant for early intervention and antimicrobial stewardship (AS) strategies before genuine MDRP isolation. The management of pre-MDRP may be more important than that of MDRP, which is a serious concern world-wide.

In these situations, some novel diagnostic and treatment methods, including novel biomarkers and phage therapy, have been investigated,[7,8] and macrolides such as erythromycin (EM), clarithromycin (CAM), and azithromycin (AZM) are considered

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effective in a broad group of patients with bronchiectasis who are at high risk of exacerbations, including patients with chronic *P. aeruginosa* infections, patients with airway infections caused by other pathogens, and those without evidence of airway infection.[9] Adult bronchiectasis guidelines support the use of long-term macrolides in patients at high risk of exacerbations, and benefit has also been seen in subgroups with *P. aeruginosa*; however, guidelines also emphasize excluding nontuberculous mycobacteria (NTM) and monitoring safety.[9–11] Furthermore, in adults with chronic *P. aeruginosa* infection, long-term inhaled antibiotics such as tobramycin (TOB) also have an important role.[12] Pediatric evidence suggests potential benefit, but the literature remains less standardized, and a review explicitly noted that no universally applicable pediatric guideline/consensus exists.[13]

In this report, two cases, one of MDRP pneumonia and one of pre-MDRP pneumonia, are presented. Both patients received excessive antibiotic treatment, and the MDRP and pre-MDRP were isolated later. However, long-term, low-dose macrolide antibiotic treatment improved repeated exacerbations and severe inflammatory status without excessive broad-spectrum antibiotic use. Both cases received CAM rather than AZM because, in Japan, CAM has been more available for a long time at the bedside and is trusted for maintaining cases with diffuse panbronchiolitis (DPB) and sinobronchial syndromes.[14–16] These patients were selected as long-term macrolide users and were followed for six months as outpatients, for a total of seven to nine months.

The minimum inhibitory concentrations (MICs) of isolated bacteria were determined by a Phenix M-50 system (Becton Dickinson, Franklin Lakes, NJ, USA) and Lysys@S4 (Shimazu Diagnostics, Tokyo, Japan) based on the broth microdilution method.

This study was approved by the Institutional Review Board (IRB) of Saitama Medical University International Medical Center (Hidaka City, Saitama, Japan) on September 07, 2022 (Approved number: #2022-072), and registered in UMIN (University hospital Medial Information Network, Tokyo, Japan) as UMIN000047992. Written, informed consent for publication of case details, such as background, physical examinations, laboratory data, and accompanying images were obtained from the adult patient and from the parent of the minor patient in accordance with the Declaration of Helsinki and the regulation of our hospital (Saitama Medical University International Medical Center).

Case Series

Case 1

A 78-year-old man who had undergone surgery for esophageal cancer developed pneumonia. His renal condition was stable, with an estimated glomerular filtration rate (eGFR) of 121 mL/min/1.73 m^2. *P. aeruginosa*, which showed good susceptibility to most antibiotics before the operation (day 0) (Table 1), was isolated and treated with meropenem (MEPM) 1 g three times per day by drip infusion intravenously (div). He had a history of div treatment with sulbactam/ampicillin for two weeks because of bacteremia caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) about one month earlier. His condition and pneumonia improved two weeks after the start of MEPM administration (day 14), and MEPM was discontinued. However, his inflammation status and chest X-ray findings again worsened on day 21 (Figure 1A), and MEPM was restarted. MEPM was administered for seven days, followed by ciprofloxacin (CPFX) 300 mg div once a day, but his respiratory and inflammatory status did not show any improvement by day 35. *P. aeruginosa* was again isolated from his sputum, and it showed resistance to the most common antibiotics, including MEPM and CPFX, indicating MDRP (Table 1). Therefore, tazobactam/ceftolozane (TAZ/CTLZ) 0.5 g three times div per day was administered. Ten days later (day 45), his inflammatory status and chest X-ray findings improved (Figure 1B). Although he could not take medication orally or by inhalation, CAM 200 mg once per day via nasogastric tube, as a long-term, low-dose macrolide therapy, was then started, and his inflammatory status and chest X-ray findings remained stable for more than six months. Additional antimicrobial therapy was not needed until day 270 during outpatient follow-up every two weeks. CAM-resistant pathogens, including non-tuberculous mycobacteria (NTM) and mycoplasma, were not isolated. No adverse effects, including severe diarrhea and QT extension on the electrocardiogram, were observed.

Case 2

A five-year-old girl with a history of surgery for congenital heart abnormalities, including transposition of the great arteries (TGA) and ventricular septal defect (VSD), was admitted for repeated episodes of bronchopneumonia. She had

Table 1 Antibiotic Susceptibility of *Pseudomonas aeruginosa* Isolated from Patient 1

	Day 0 MIC	S/I/R	Day 35 MIC	S/I/R
AZT	8	S	>16	R
PIPC	4	S	32	I
PIPC/TAZ	≦4	S	16	S
IPM	1	S	>8	R
MEPM	0.25	S	>8	R
CAZ	4	S	16	R
CFPM	2	S	16	I
CTLZ/TAZ	≦1/4	S	≦4/4	S
AMK	≦4	S	>32	R
GM	≦2	S	>8	R
MINO	>8	R	≦1	R
LVFX	1	S	>4	R
CPFX	0.25	S	>4	R
ST	80	R	80	R

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; AZT, aztreonam; PIPC, piperacillin; PIPC/TAZ, piperacillin/tazobactam; IPM, imipenem; MEPM, meropenem; CAZ, ceftazidime; CFPM, cefepime; CTLZ/TAZ, ceftolozane/tazobactam; AMK, amikacin; GM, gentamycin; MINO, minocycline; LVFX, levofloxacin; CPFX, ciprofloxacin; ST, Sulfamethoxazole/trimethoprim.

been admitted three times in the past year due to pneumonia and had received antibiotic treatment with MEPM three times per day for 10–14 days by div on each admission.

On admission, increased opacity was observed in the right lung field on chest radiography (Figure 2A), and the arterial oxygen saturation (SpO_2) was 93% (O_2 6-L mask). *P. aeruginosa* which showed good susceptibility to the antibiotics (Table 2) was isolated, and MEPM div three times per day and high-flow nasal cannula (HFNC) management were initiated (day 0). Laboratory data on day 0 were as follows: white blood cell (WBC) count, 14.20 × 10^3/μL,

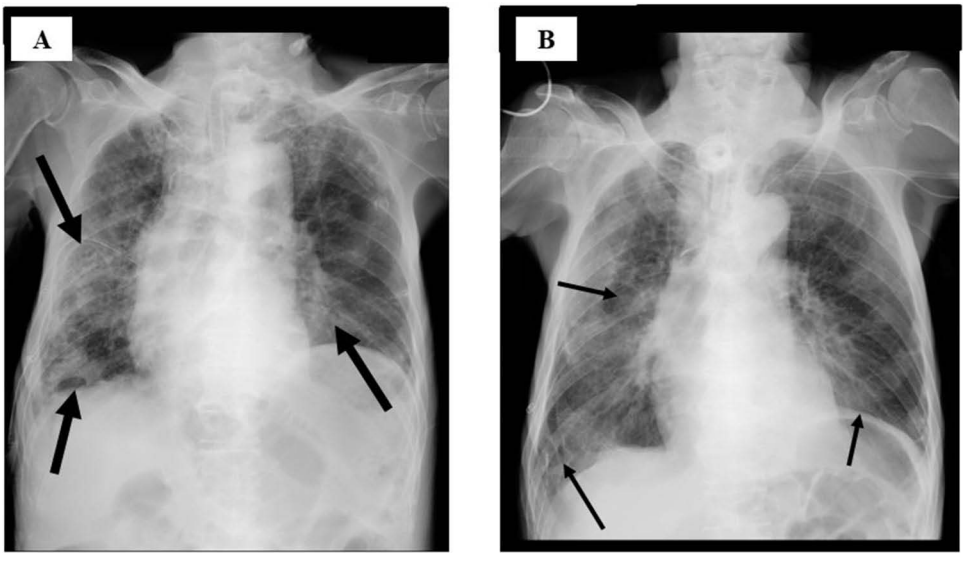

Figure 1 Chest X-ray findings of Patient 1 on Day 21 (**A**) and Day 45 (**B**). Lung opacity, infiltrates, and volumes are improved after 24 days of treatment (arrows). The improved lung condition then becomes stable for more than six months with clarithromycin 200 mg once per day, as a long-term, low-dose treatment, and additional antimicrobial therapy was not needed until day 270.

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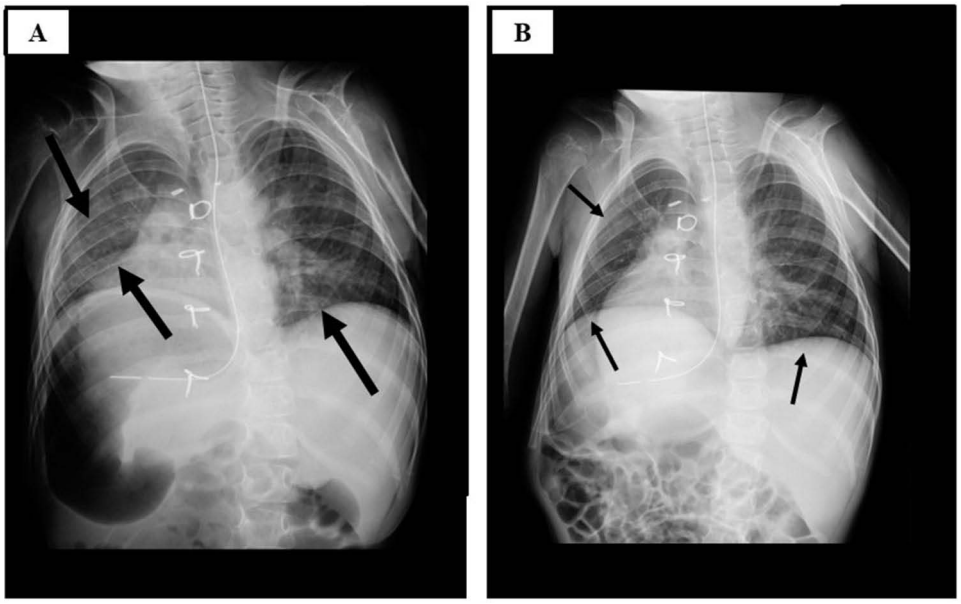

Figure 2 Chest X-ray findings of Patient 2 on admission (Day 0) (**A**) and Day 20 (**B**). Lung permeability and shadows are improved after 20 days of treatment (arrows). The improved lung condition then becomes stable for more than six months with clarithromycin 5 mg/kg three times per day as long-term, low-dose treatment, and additional antimicrobial therapy was not used until day 220.

with 82.2% neutrophils, 11.7% lymphocytes, 3.7% monocytes, 1.9% eosinophils, and 0.5% basophils; platelet count, $32.1 \times 10^4/\mu L$; hemoglobin, 14.0 g/dL; blood urea nitrogen, 10.7 g/L; serum creatinine, 0.17 mg/dL; aspartate aminotransferase (AST), 17 U/L; alanine aminotransferase (ALT), 20 U/L; and C-reactive protein (CRP), 16.20 mg/dL.

Table 2 Antibiotic Susceptibility of *Pseudomonas aeruginosa* Isolated from Patient 2

	Day 0 MIC	**S/I/R**	**Day 10 MIC**	**S/I/R**
AZT	8	S	>16	R
PIPC	4	S	64	I
PIPC/TAZ	≦4	S	64	I
IPM	1	S	>8	R
MEPM	0.25	S	>8	R
CAZ	4	S	16	R
CFPM	2	S	16	I
CTLZ/TAZ	≦1/4	S	≦1/4	S
AMK	≦4	S	≦4	S
GM	≦2	S	≦2	S
MINO	>8	R	>8	R
LVFX	1	S	4	I
CPFX	0.25	S	1	S
ST	80	R	80	R

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; AZT, aztreonam; PIPC, piperacillin; PIPC/TAZ, piperacillin/tazobactam; IPM, imipenem; MEPM, meropenem; CAZ, ceftazidime; CFPM, cefepime; CTLZ/TAZ, ceftolozane/tazobactam; AMK, amikacin; GM, gentamycin; MINO, minocycline; LVFX, levofloxacin; CPFX, ciprofloxacin; ST, Sulfamethoxazole/trimethoprim.

After 10 days, her condition, including respiratory status and laboratory data, worsened, and pre-MDRP, which showed good susceptibility to aminoglycosides, but resistance to MEPM, was isolated from her sputum (day 10) (Table 2). Her chest X-ray did not improve, and CPFX was started once per day by div, because the isolated pre-MDRP showed susceptibility to CPFX, but only intermediate susceptibility to levofloxacin (LVFX). On day 20, her respiratory condition, including chest X-ray findings, improved (Figure 2B). Although she could not take medication orally or by inhalation, half-dose (5 mg/kg) CAM three times per day via nasogastric tube was started as long-term, low-dose macrolide therapy, and her inflammatory status and chest X-ray findings remained stable for more than six months. Additional antimicrobial therapy was not given until day 220 during outpatient follow-up every two weeks. CAM-resistant pathogens, including NTM and mycoplasma, were not isolated. No adverse effects, including severe diarrhea and QT extension on the electrocardiogram, were observed.

Discussion

P. aeruginosa is an opportunistic pathogen responsible for ventilator-associated pneumonia (VAP) and chronic respiratory infections with bronchiectasis. These respiratory infections due to *P. aeruginosa* are usually multidrug-resistant, are associated with severe infection and increased mortality, and have been associated with higher rates of treatment failure, relapse, and death.[17]

In the present report, two cases that received repeated and/or long-duration antibiotics were included. Both patients experienced repeated exacerbations, although broad-spectrum antibiotics were administered. However, they were well maintained, and exacerbations were prevented by long-term, low-dose macrolide therapy.

Macrolides might be the most commonly used antibiotics for the treatment of infections. They have an inhibitory effect on a variety of respiratory pathogens; in addition, they have non-anti-infective effects, including anti-inflammatory effects, regulation of airway secretion, immune regulation, and other effects. Therefore, long-term, low-dose macrolide use is recommended for both adults and children.[9,13]

In adults, a strong recommendation has been supported by a highly clinically relevant reduction in exacerbations and a highly meaningful improvement in quality of life with long-term macrolide treatment.[10] The trials showed no major safety concerns, and in studies lasting 6 to 12 months, antimicrobial resistance was not identified as a significant issue. The largest studies included patients with ≥1 or ≥3 exacerbations per year, and benefits were demonstrated across multiple patient subgroups, including those with low exacerbation frequency and a subgroup of patients with *P. aeruginosa* infections.[9,10]

In the present adult case, the patient was actually maintained for about six to nine months by 200 mg per day administration without additional broad-spectrum antibiotic use, and CAM-resistant pathogens, including NTM, were not isolated, although CAM was usually used at 400 mg per day for a few days to treat the acute infection. Since he could not take medication orally or by inhalation, he could not take TOB by inhalation, but CAM administration via a nasogastric tube was possible. CAM administration might be beneficial as an alternative agent for such patients in poor condition with limitations of oral intake.

Furthermore, in children, a growing number of studies have shown that the non-anti-infective effects of macrolides have important and potential value in the treatment of pediatric chronic airway diseases; the therapy was described as "long-term, low-dose usage."[13] In children, CAM was usually administered at 10 mg/kg for acute infectious diseases, including mycoplasma, for a short term, such as 7–10 days, but it has been suggested that anti-inflammatory effects and regulation of airway secretions occur through mechanisms such as regulation of cell signaling and interference with inflammatory cells and cytokines when CAM is given at 5 mg/kg for several months, as in the present pediatric case.[13] Immunomodulatory-related antimicrobial effects due to inhibition of microbial adhesion, virulence factors, biofilms, and quorum sensing systems have also been suggested, as in adults.[9,13]

In the present cases, CAM was used to manage repeated chronic respiratory infections due to MDRP and pre-MDRP, although AZM has usually been used worldwide.[9,10,13] CAM is a 14-membered-ring macrolide, and AZM is a 15-membered-ring macrolide; however, CAM has also been reported to be well tolerated, with anti-inflammatory and bacteriostatic effects in chronic *P. aeruginosa* infections, especially in Japan.[18,19] We have also observed that CAM could overproduce muc5ac core protein in a murine model of DPB that was similar to cystic fibrosis and usually had chronic pre-MDRP infections.[14] CAM could be used for the management of chronic *P. aeruginosa* infection and inhibit MDRP and pre-MDRP isolation due to excessive and inappropriate broad-spectrum antibiotic use.

As a limitation, long-term macrolide therapy is widely recognized to contribute to macrolide resistance in commensal and pathogenic bacteria. In the present cases, no pathogenic bacteria including NTM and mycoplasma were isolated 6–12 months after long-term, low-dose CAM was administered. However, since there were only two patients in this case series, it is difficult to draw firm conclusions from them in the absence of controls and comparators. Furthermore, it could not be proven directly that CAM treated the acute infection, prevented future resistance emergence, or inhibited colonization. Long-term follow-up data are needed to assess recurrence, persistence, or outcomes following discharge to clarify the microbiological mechanisms of long-term, low-dose CAM for recurrent and resistant *P. aeruginosa* infection.

Conclusions

In conclusion, two cases of recurrent/refractory chronic respiratory infection due to MDRP and pre-MDRP in which drug susceptibility was evaluated were presented. The adult MDRP case and the pediatric pre-MDRP case were maintained by long-term, low-dose macrolide therapy with CAM, which was used at half doses compared with regular use for acute infection, and recommended for chronic patients with bronchiectasis, especially in Japan. Macrolides might be useful to prevent the development of resistant pathogens because they have non-anti-infective effects, including anti-inflammatory effects. The recommendations for their use have been supported by a highly clinically relevant reduction in exacerbations. More detailed, large, long-term, studies are needed to confirm the clinical effects of long-term, low-dose macrolides in adults and children.

Disclosure

The author reports no conflicts of interest in this work.

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