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ORIGINAL ARTICLE

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Visualization of cross-resistance between antimicrobial agents by asymmetric multidimensional scaling

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Abstract

What is known and objective: In our previous studies, we developed a cross-resistance rate (CRR) correlation diagram (CRR diagram) that visually captures the magnitude of CRRs between antimicrobials using scatter plots. We used asymmetric multidimensional scaling (MDS) to transform cross-resistance similarities between antimicrobials into a 2-dimensional map and attempted to visually express them. We also explored the antibiograms of Pseudomonas aeruginosa before and after the transfer to newly built hospitals, and we determined by the CRR diagram that the CRRs among β-lactam antimicrobials other than carbapenems decreased substantially with the facility transfer. The present study tests whether the analysis of CRRs by asymmetric MDS can be used as new visual information that is easy for healthcare professionals to understand.

Method: We tested the impact of changes in the nosocomial environment due to institutional transfers on CRRs among antimicrobials in asymmetric MDS, as well as contrasted the asymmetric MDS map and CRR diagram.

Results and Discussion: In the asymmetric MDS map, antimicrobial groups with the same mechanism of action were displayed close together, and antimicrobial groups with different mechanisms of action were displayed separately. The asymmetric MDS map drawn solely for antimicrobials belonging to the group with the same mechanism of action showed similarities to the CRR diagram. Also, the distance of each antimicrobial to other antimicrobials shown in the asymmetric MDS map was negatively correlated with the CRRs for them against that antimicrobial.

What is new and conclusion: The asymmetric MDS map expresses the dissimilarity as distances between agents, and there are no meanings or units on the ordinate and abscissa axes of the output map. In contrast, the CRR diagram expresses the antimicrobials' resistance status as values, such as resistance rate and CRR. By analysing the CRRs in the asymmetric MDS, it is feasible to visually recognize cross-resistance similarities between antimicrobial groups as distances. The use of the asymmetric MDS

combined with the CRR diagram allows us to visually understand the resistance and cross-resistance status of each antimicrobial agent as a 2-dimensional map, as well as to understand the trends and characteristics of the data by means of quantitative values.

KEYWORDS
antimicrobial, asymmetric MDS, cross-resistance, CRR diagram, hospital, *Pseudomonas aeruginosa*

1 | INTRODUCTION

The emergence of antibiotic-resistant bacteria has become a global problem. Monitoring the status of antimicrobial resistance is important to select effective antimicrobials in treating infectious diseases. Numerous hospitals have prepared antibiograms to monitor antimicrobial susceptibility rates, thereby contributing to the proper use of antimicrobials.[1–4] The cross-resistance rate (CRR) should also be an important reference factor when multiple antimicrobials are used for severe infections suspected to be caused by multidrug-resistant bacteria; however, it is not as actively employed in hospitals as the susceptibility rate.

We had previously developed a CRR matrix in which CRRs between antimicrobials are drawn as square matrices, as well as a CRR correlation diagram (CRR diagram), which is a plot diagram that can easily determine the similarities in sensitivity and cross-resistance between antimicrobials.[5]

Multidimensional scaling (MDS) is a statistical technique that reveals relationships among objects hidden behind data by transforming the data that shows similarities into a multidimensional map and visually representing the relationships. MDS has been used in psychology, sociology and marketing.[6–8] In the medical field, MDS has been used to show the (dis)similarity of individual organisms, such as viruses and cancer cells, from DNA sequences and clinical information.[9–12]

By considering the CRR matrix as the accumulation of asymmetric similarity data, we applied the analytical method developed by Okada and Imaizumi, "asymmetric MDS based on the distance-radius model,"[13] to the analysis of the CRR matrix. The results showed that processing the CRR matrix with asymmetric MDS could show the similarities between antimicrobial groups as a 2-dimensional map.[14]

On 1 July 2015, Sakai City Medical Center was moved to its current location, approximately 3.5 km away from its original location, a relocation that led to a significant turnover of outpatients and inpatients; the bacterial flora inhabiting the centre and its surroundings is also likely to have changed significantly.[15,16] We confirmed the impact of the hospital relocation on bacterial flora[17] and found that it is feasible to visualize and capture the changes in CRRs using CRR diagrams.[18]

In this study, we tested whether it is possible to capture changes in cross-resistance among antimicrobials due to hospital relocation by asymmetric MDS. We also discuss the possibility that the analysis of CRRs by asymmetric MDS could be a valuable visual information tool for healthcare professionals by contrasting the MDS with the CRR diagram.

2 | METHODS

2.1 | Data

We collected the minimum inhibitory concentration data of each antimicrobial against *P. aeruginosa* isolated and subjected to drug susceptibility testing at Sakai City Medical Center.[18] The data were collected over 6 years, from January 2013 to December 2018. The antimicrobials included were those for which drug susceptibility testing was performed for *P. aeruginosa* (Table 1).

The minimum inhibitory concentration data were determined as susceptible (S), intermediate (I) or resistant (R), according to the Clinical and Laboratory Standards Institute criteria (M100-S26).[19]

To ensure a minimum of 10 resistant strains for the CRR denominator, we provided a data aggregation period of 18 months, which was divided into five segments: b1 and b2, which were prior to the hospital relocation, and a1, a2 and a3, which were after the hospital relocation (Figure 1).

Only the first visit data were used for the analysis of patients who underwent multiple drug susceptibility testing.[20]

TABLE 1 Classification of the assessed antimicrobial agents and their abbreviations

Penicillins*		**Monobactams***	
Piperacillin	PIPC	Aztreonam	AZT
Piperacillin/Tazobactam	PIPC/TAZ		
Cephalosporins*		**Aminoglycosides**	
Ceftazidime	CAZ	Amikacin	AMK
Cefepime	CFPM	Gentamicin	GM
Cefoperazone/Sulbactam	CPZ/SBT		
Carbapenems*		**Fluoroquinolones**	
Imipenem	IPM	Ciprofloxacin	CPFX
Meropenem	MEPM	Levofloxacin	LVFX

*β-lactams.

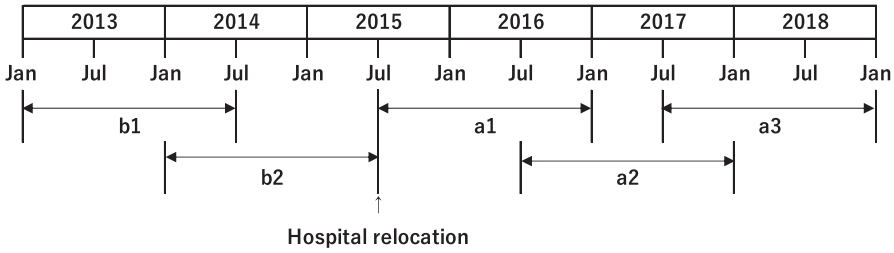


FIGURE 1 Segments of the data aggregation period

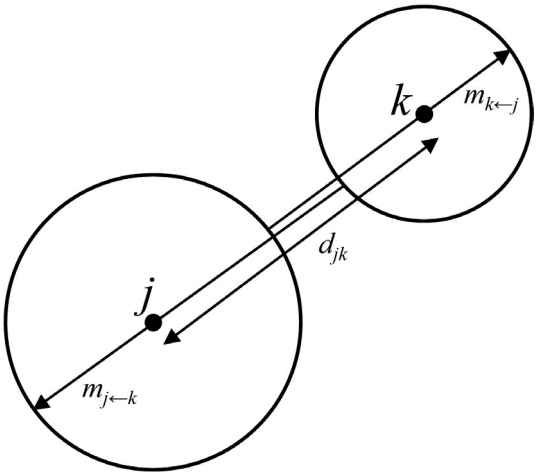


FIGURE 2 Conceptual diagram of the distance-radius model

2.2 | Resistance and cross-resistance rates

In clinical practice, an antimicrobial judged "intermediate" by susceptibility testing is rarely used to treat infections caused by the bacterium. In this study, we therefore considered the strains that were intermediate to be resistant and employed them for the calculations.

When the number of strains resistant to the base antimicrobial B that are also resistant to another antimicrobial X is set to $N(R_B \bigcap Rx)$, the $CRR_{B\leftarrow X}$ (%) of antimicrobial X to the base antimicrobial B is calculated using the following formula:

$$CRR_{B\leftarrow X} = \frac{N(R_B \cap R_X)}{N(R_B)} \times 100. \quad (1)$$

2.3 | Cross-resistance rate matrix

The CRR matrix is a square matrix with antimicrobials arranged in rows and columns, and the cells in each row display $CRR_{B\leftarrow X}$ (%) of antimicrobials X arranged in columns to the base antimicrobials B arranged in rows. The CRR matrix in the b1 segment is shown as an example (Table 1; see Table A1 in Appendix for CRR matrices in all segments).

2.4 | Cross-resistance rate correlation diagram

The CRR diagram is a scatter plot showing the CRR between each antimicrobial in a given bacterium; the horizontal axis represents the CRR ($CRR_{B\leftarrow X}$) against the base antimicrobial B for antimicrobial X, and the vertical axis represents the CRR ($CRR_{X\leftarrow B}$) against antimicrobial X for the base antimicrobial B.

2.5 | Asymmetric multidimensional scaling based on the distance-radius model

When the (dis)similarities between multiple objects are given in numeric terms, MDS considers the objects as plots arranged in a multidimensional space and produces maps with similar objects placed closer and dissimilar objects placed farther apart. In a normal MDS, data similarity is represented by distance, and in general, the distance between A and B is equal to the distance between B and A. Therefore, the similar data to be handled should be mutually symmetric.

In CRR, however, $CRR_{A\leftarrow B}$ and $CRR_{B\leftarrow A}$ are almost always different. Therefore, this study analysed CRR matrices using asymmetric MDS based on the distance-radius model,[13] which is a modified form of MDS and can handle asymmetric similarity data.

Asymmetric MDS is shown schematically in Figure 2. If the distance between the centre of each circle is d_{jk} where there is an object j and k, the distance $m_{k\leftarrow j}$ of k from j is the distance from the end of the circle j to the end of the circle k through the centre of k and can be expressed by the following equation (2):

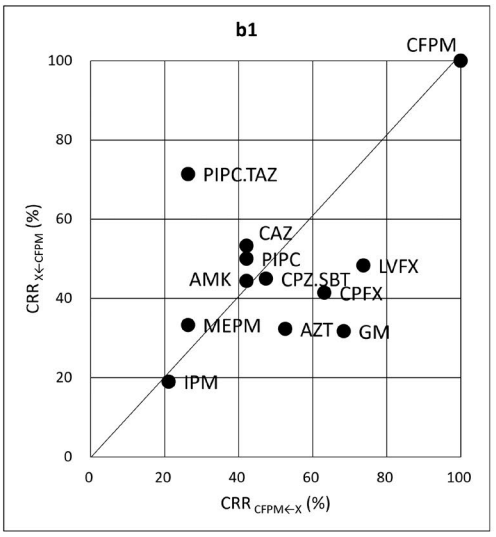
$$m_{h\leftarrow j} = d_{jk} - r_j + r_k. \quad (2)$$

Thus, asymmetric MDS is a model that expresses asymmetric relations in terms of the length of the circles' radii.

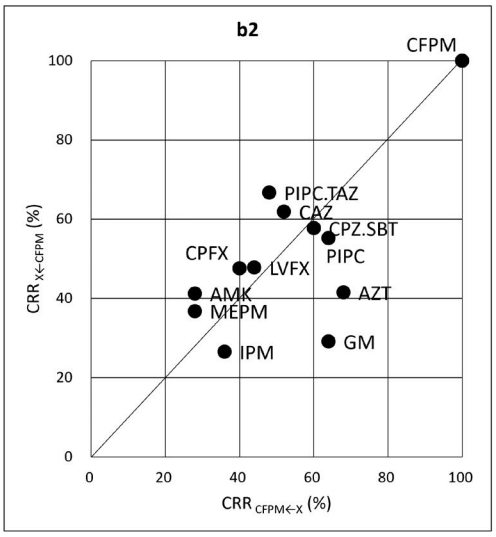
For each segment, we created a CRR matrix for the target antimicrobial using the plug-in developed by Imaizumi, which can run asymmetric MDS (under a Euclidean distance metric) on R, a software environment for statistical computing. Euclidean distance was adopted as the distance.

2.6 | Similarities in cross-resistance between the cross-resistance rate correlation diagram and the asymmetric multidimensional scaling map

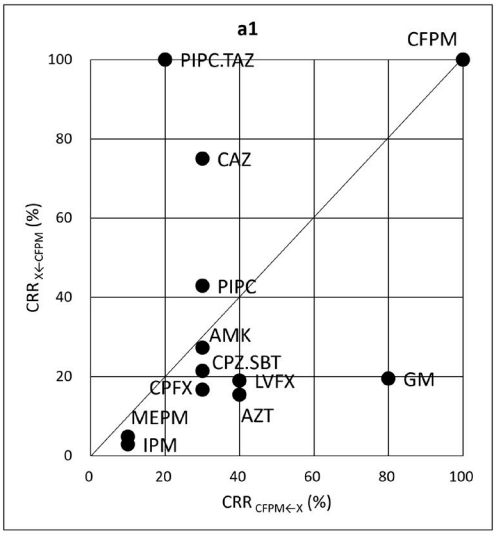
In the CRR diagram, the antimicrobial is plotted close to the upper right corner if the cross-resistance between the antimicrobial and



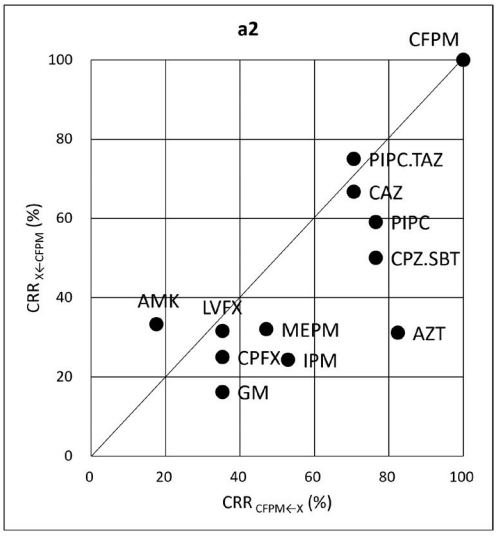
1. b1 (2013-01 ~ 2014-06)



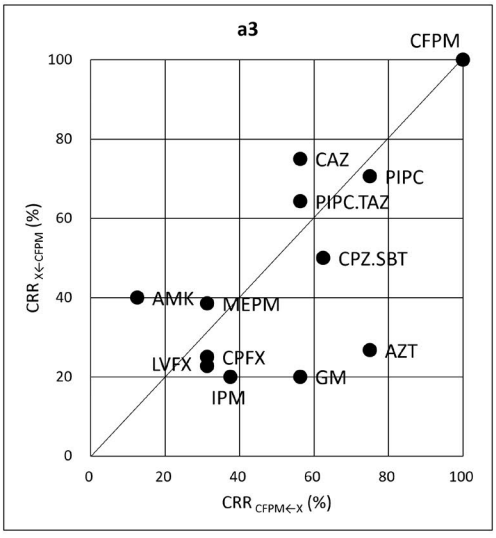
2. b2 (2014-01 ~ 2015-06)



3. a1 (2015-07 ~ 2016-12)

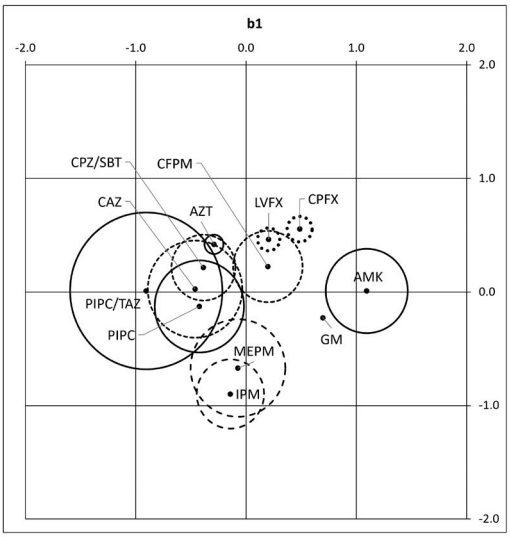


4. a2 (2016-07 ~ 2017-12)

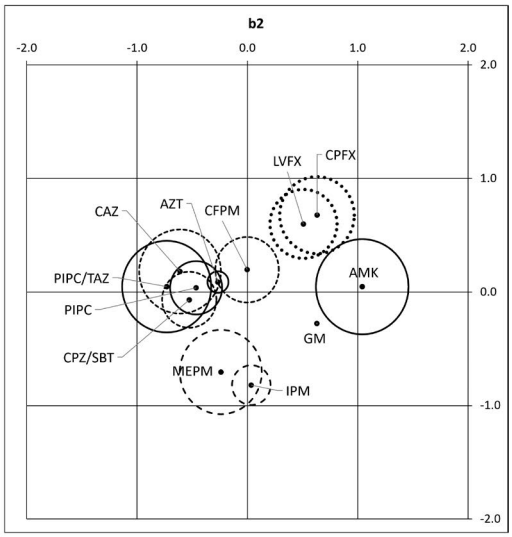


5. a3 (2017-07 ~ 2018-12)

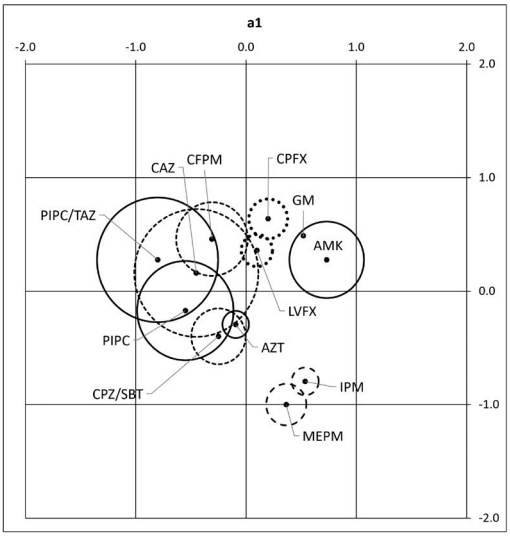
FIGURE 3 Cross-resistance rate correlation diagram using cefepime as the base antimicrobial in each segment



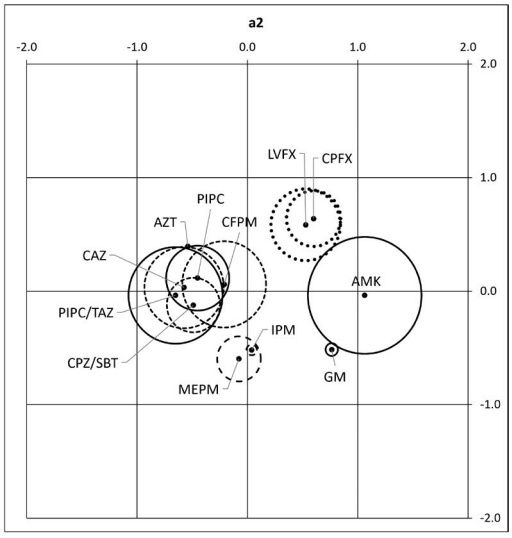
1. b1 (2013-01 ~ 2014-06)



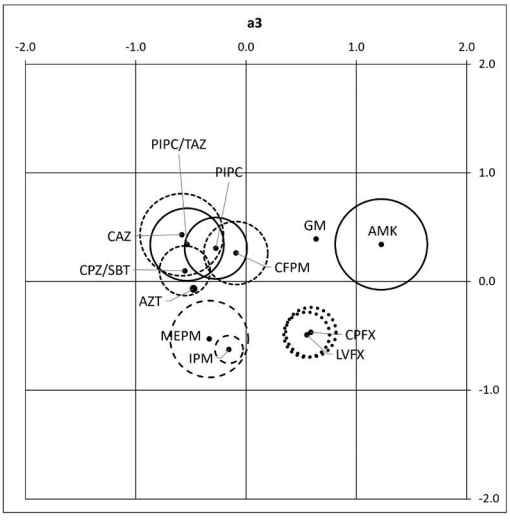
2. b2 (2014-01 ~ 2015-06)



3. a1 (2015-07 ~ 2016-12)



4. a2 (2016-07 ~ 2017-12)



5. a3 (2017-07 ~ 2018-12)

FIGURE 4 Asymmetric multidimensional scaling maps in each segment

TABLE 2 Cross-resistance rate matrix in b1 segment

Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	37.5 (6/16)	62.5 (10/16)	68.8 (11/16)	50 (8/16)	43.8 (7/16)	43.8 (7/16)	81.3 (13/16)	18.8 (3/16)	50 (8/16)	31.3 (5/16)	50 (8/16)
PIPC/TAZ	85.7 (6/7)	–	100 (7/7)	71.4 (5/7)	71.4 (5/7)	42.9 (3/7)	42.9 (3/7)	85.7 (6/7)	0 (0/7)	42.9 (3/7)	28.6 (2/7)	57.1 (4/7)
CAZ	66.7 (10/15)	46.7 (7/15)	–	73.3 (11/15)	53.3 (8/15)	40 (6/15)	40 (6/15)	73.3 (11/15)	20 (3/15)	46.7 (7/15)	40 (6/15)	60 (9/15)
CPZ/SBT	55 (11/20)	25 (5/20)	55 (11/20)	–	45 (9/20)	30 (6/20)	35 (7/20)	85 (17/20)	15 (3/20)	40 (8/20)	40 (8/20)	60 (12/20)
CFPM	42.1 (8/19)	26.3 (5/19)	42.1 (8/19)	47.4 (9/19)	–	21.1 (4/19)	26.3 (5/19)	52.6 (10/19)	42.1 (8/19)	68.4 (13/19)	63.2 (12/19)	73.7 (14/19)
IPM	33.3 (7/21)	14.3 (3/21)	28.6 (6/21)	28.6 (6/21)	19 (4/21)	–	52.4 (11/21)	33.3 (7/21)	19 (4/21)	33.3 (7/21)	28.6 (6/21)	33.3 (7/21)
MEPM	46.7 (7/15)	20 (3/15)	40 (6/15)	46.7 (7/15)	33.3 (5/15)	73.3 (11/15)	–	40 (6/15)	26.7 (4/15)	46.7 (7/15)	46.7 (7/15)	46.7 (7/15)
AZT	41.9 (13/31)	19.4 (6/31)	35.5 (11/31)	54.8 (17/31)	32.3 (10/31)	22.6 (7/31)	19.4 (6/31)	–	16.1 (5/31)	32.3 (10/31)	35.5 (11/31)	48.4 (15/31)
AMK	16.7 (3/18)	0 (0/18)	16.7 (3/18)	16.7 (3/18)	44.4 (8/18)	22.2 (4/18)	22.2 (4/18)	27.8 (5/18)	–	94.4 (17/18)	50 (9/18)	44.4 (8/18)
GM	19.5 (8/41)	7.3 (3/41)	17.1 (7/41)	19.5 (8/41)	31.7 (13/41)	17.1 (7/41)	17.1 (7/41)	24.4 (10/41)	41.5 (17/41)	–	24.4 (10/41)	26.8 (11/41)
CPFX	17.2 (5/29)	6.9 (2/29)	20.7 (6/29)	27.6 (8/29)	41.4 (12/29)	20.7 (6/29)	24.1 (7/29)	37.9 (11/29)	31 (9/29)	34.5 (10/29)	–	86.2 (25/29)
LVFX	27.6 (8/29)	13.8 (4/29)	31 (9/29)	41.4 (12/29)	48.3 (14/29)	24.1 (7/29)	24.1 (7/29)	51.7 (15/29)	27.6 (8/29)	37.9 (11/29)	86.2 (25/29)	–

the base antimicrobial is similar and is plotted closer to the origin if not similar.

In the MDS map, on the contrary, dissimilarity is represented by the distance between plots. If the CRR is regarded as the similarity between antimicrobials, antimicrobial clusters are closer to each other with a larger CRR and are plotted apart between antimicrobials with a smaller CRR of each other.

2.7 | Symmetry of cross-resistance in the cross-resistance rate correlation diagram and asymmetric multidimensional scaling placements

If $CRR_{B\leftarrow X}$ and $CRR_{X\leftarrow B}$ are equal, then the resistance of both antimicrobials is symmetric; if they are very different, the resistance is asymmetric, that is, the coordinates of antimicrobial X in the CRR diagram with antimicrobial B as the reference are plotted near the diagonal if the resistance of both antimicrobials shows symmetry and away from the diagonal if they show asymmetry.

In contrast, in the asymmetric MDS model, an asymmetric association is expressed by the length of the circle's radius. In this study, the more symmetric the cross-resistance of both antimicrobials, the smaller the radius of the circle displayed. In other words, the greater the asymmetry, the greater the radius.

3 | RESULTS

3.1 | Cross-resistance rate matrix

For PIPC/TAZ in the b1 segment, CAZ, PIPC and PIPC/TAZ in the a1 segment, and AMK in the a2 and a3 segments, fewer than 10 resistant specimens were collected. The calculated CRR is therefore unreliable and should be considered when it is clinically captured.

3.2 | Cross-resistance rate correlation diagram

When a CRR diagram is drawn by setting an antimicrobial with an extremely large or small CRR as the base antimicrobial, many of the other antimicrobial points are localized in one corner, making it difficult to visually identify changes in coordinates. We therefore drew a CRR diagram using CFPM as a base antimicrobial, which has a CRR located in the middle and does not assume an extreme value out of the target antimicrobials.

Figure 3 shows the CRR diagram with CFPM as the base antimicrobial in each segment.

When the CRR diagram is to show the base antimicrobial, it will be plotted in the upper right corner ($CRR_{CFPM\leftarrow X}$ 100%, $CRR_{X\leftarrow CFPM}$ 100%). In this study, the base antimicrobials are displayed to compare with the asymmetric MDS map where all the antimicrobials are plotted.

TABLE 3 Radii of circles for each antimicrobial agent in the asymmetric multidimensional scaling map in each segment

	Radii of the circles for each antimicrobial agent					
	Segment	**b1**	**b2**	**a1**	**a2**	**a3**
Antimicrobial	PIPC	0.405	0.235	0.436	0.286	0.283
	PIPC/TAZ	0.691	0.404	0.549	0.426	0.334
	CAZ	0.428	0.371	0.562	0.359	0.378
	CPZ/SBT	0.290	0.247	0.246	0.241	0.229
	CFPM	0.315	0.288	0.325	0.381	0.290
	IPM	0.305	0.174	0.122	0.047	0.127
	MEPM	0.429	0.372	0.182	0.198	0.353
	AZT	0.085	0.095	0.120	0.000	0.028
	AMK	0.371	0.419	0.338	0.514	0.417
	GM	0.000	0.000	0.000	0.056	0.000
	CPFX	0.113	0.338	0.175	0.245	0.229
	LVFX	0.101	0.304	0.141	0.315	0.208

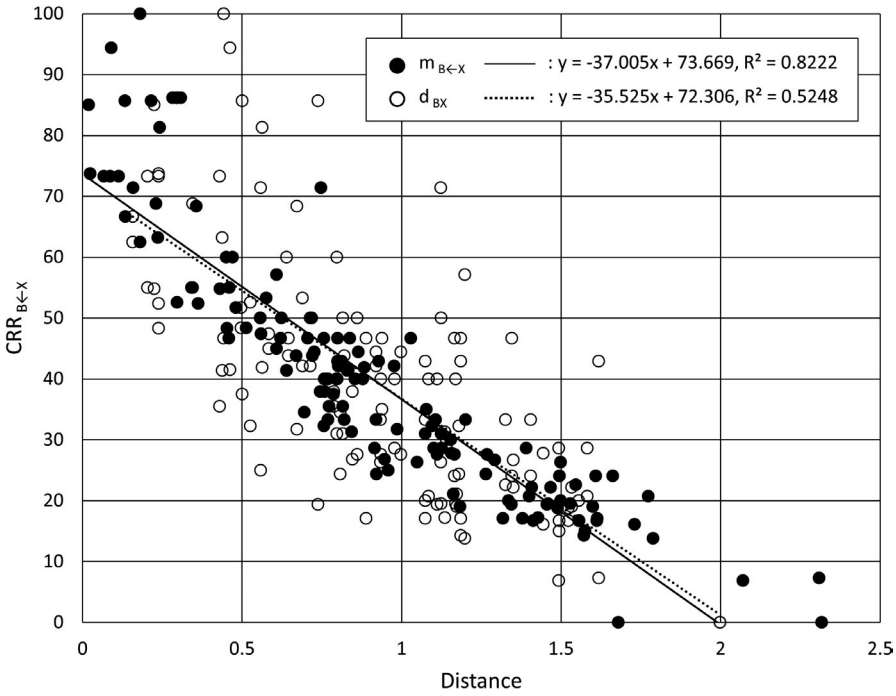


FIGURE 5 Relationship between the cross-resistance rate and the distance between plots of antimicrobials (*d*) and the distance corrected by the radius of the circle (*m*) in asymmetric multidimensional scaling (R: Pearson's product-moment correlation)

3.3 | Asymmetric multidimensional scaling

In asymmetric MDS, circles representing the asymmetry of similarity are displayed along with points for each element. Figure 4 shows the asymmetric MDS maps of each segment drawn based on Table 2.

In MDS, it is possible to rotate the whole map around the origin or invert it into the mirror image. Therefore, for an easier comparison of each antimicrobial arrangement, the plot set the line connecting the AMK and PIPC/TAZ plots in all figures to be horizontal, and the IPM and MEPM plots to be below those 2 antimicrobials.

When compressing dimensions in MDS, a numerical value called stress is used as a measure of how well the distance between objects corresponds to the similarity between them.[21] According to the pre-examination of the stress obtained by the analyses from 5-dimensional through unidimensional spaces, we noticed that the 2D presentation is the most appropriate for all five data sets. As to the value of stress, a lower stress is better for evaluating the data characteristics, ideally being 0.2 or less. In the results, the stress values in 2 dimensions of the data for the b1-a3 segments are 0.1262, 0.0687, 0.1751, 0.1160 and 0.1333 respectively. As shown in Figure 4, all the values are less than 0.2 (See Figure A1 in Appendix for the stress values in all dimensions).

3.4 | Radii of the circles in the asymmetric multidimensional scaling map

The radii of the circles in the asymmetric MDS map are shown in Figure 4 and Table 3 for each segment.

For X and B shown on the asymmetric MDS maps, the distance from B to X is obtained by correcting the distance between the centres of the circles by the radii of the circles as shown in equation 2.

For all antimicrobial combinations, $CRR_{B\leftarrow X}$, d_{BX} and $m_{X\leftarrow B}$ were calculated for each segment. Pearson's correlation coefficients between $CRR_{B\leftarrow X}$ and d_{BX} in b1, b2, a1, a2 and a3 were −0.724, −0.882, −0.598, −0.841 and −0.817 respectively; between $CRR_{B\leftarrow X}$ and $m_{X\leftarrow B}$, the coefficients were −0.907, −0.960, −0.794, −0.924 and −0.908 respectively. Figure 5 shows a scatter plot using the b1 segment data, with d_{BX} and $m_{X\leftarrow B}$ as the horizontal axis and $CRR_{B\leftarrow X}$ as the vertical axis. These values and the plot indicate that $CRR_{B\leftarrow X}$ is negatively correlated with both d_{BX} and $m_{X\leftarrow B}$, showing that $m_{X\leftarrow B}$, which is d_{BX} corrected by the circle's radius, correlates more with $CRR_{B\leftarrow X}$ than the distance between centres, d_{BX}.

3.5 | Effects of selection data on the asymmetric multidimensional scaling map

To ascertain the effect of the difference in numbers and groups of selected antimicrobials, CRR diagrams were compared with an MDS map drawn with the same antimicrobial data (Figure 6). To facilitate comparisons with CRR diagrams, circles were not shown in the asymmetric MDS map. All comparisons were made based on the data from the b1 segment.

Figure 6-1 is based on 12 antimicrobials, and the CRR diagram is drawn with CFPM as the base antimicrobial; thus, the asymmetric MDS map is also drawn so that CFPM is rotated 45 degrees from its origin.

In Figure 6-2, the composition of the antimicrobial groups was reduced, without changes, to 8 antimicrobials based on the data used in Figure 6-1.

In Figure 6-3 and 6-4, the antimicrobial group was restricted to β-lactams only, from which 8 antimicrobials were selected. Figure 6-3 was drawn with CFPM, and Figure 6-4 was drawn with CAZ as the base antimicrobial.

4 | DISCUSSION

4.1 | Cross-resistance rate correlation diagram and asymmetric multidimensional scaling map in each segment

In the CRR diagram and asymmetric MDS map, both before (b2: Figure 3-2, 4-2) and after (a1: Figure 3-3, 4-3) the hospital relocation, the antimicrobials' arrangement varied significantly, which strongly suggests that hospital relocation greatly changed the resistance of *P. aeruginosa* to the respective antimicrobials.

In the CRR diagram, β-lactam antimicrobial plots were shifted leftward significantly in the a1 segment after relocation (Figure 3-3) In particular, PIPC and CPZ/SBT moved a large distance along the diagonal to the bottom left, indicating that the CRRs between the 2 drugs and CFPM decreased, suggesting that the symmetries did not change much and that only the similarities decreased. This reduction in similarities is remarkable, and it can be confirmed that the plot spacing between these 2 antimicrobials and CFPM is increased compared with the b2 segment, even in the asymmetric MDS map (Figure 4-3).

In the CRR diagram of the a2 segment, the plots of the β-lactam antimicrobials other than carbapenems were shifted a large distance to the right and were clustered towards the centre in the longitudinal direction (Figure 3-4). This indicates that the CRR to CFPM of these antimicrobials increased simultaneously, and the variability in the CRR of CFPM to these decreased, suggesting that the similarity and symmetry among these antimicrobials increased. This finding corresponds to the fact that these antimicrobials were more clustered in the asymmetric MDS map of the a2 segment than in the a1 segment (Figure 4-4).

In the CRR diagram of the a1 segment, the carbapenem antimicrobials IPM and MEPM were plotted close to the origin, away from other antimicrobials (Figure 3-3), indicating a large reduction in the similarity between the two antimicrobials and CFPM, which can be confirmed by the large separation of both antimicrobials from other antimicrobials in the asymmetric MDS map in the a1 segment (Figure 4-3).

4.2 | Cross-resistance asymmetry

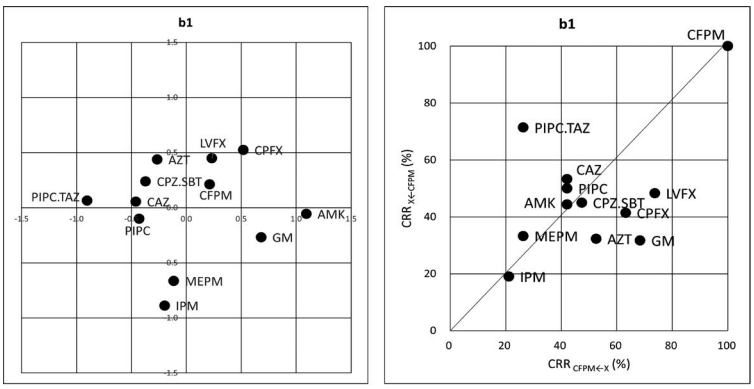
The CRR diagram of the a1 segment shows that the CRR of PIPC/TAZ and CAZ to CFPM decreased, and the CRR of CFPM to PIPC/TAZ and CAZ was elevated compared with the b2 segment (Figure 3-3). Thus, in the a1 segment, PIPC/TAZ and CAZ increased CRR asymmetry against CFPM. This finding can also be distinguished by the relatively larger radii of the circles in PIPC/TAZ and CAZ relative to the radii of the circles in CFPM in the asymmetric MDS map in the a1 segment than in the b2 segment (Figure 4-3).

The antimicrobials with the largest angle of view from the origin in each segment (ie those with low similarity to CFPM and strong asymmetry in similarity) were PIPC/TAZ in the b1 and a1 segments and AMK in the b2, a2 and a3 segments, a finding consistent with the antimicrobials with the largest circle radii in the asymmetric MDS map in cases other than the a1 segment.

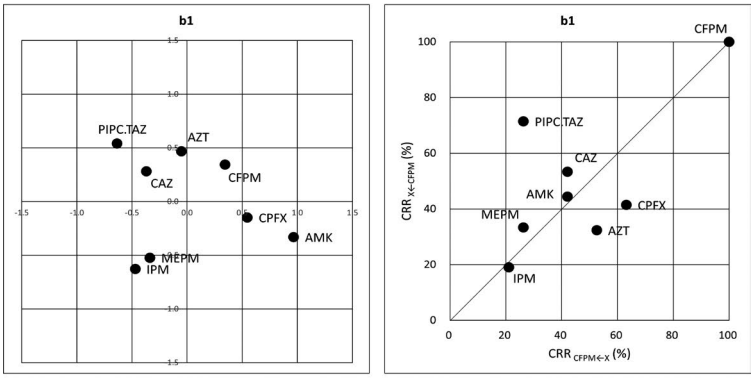
In contrast, the antimicrobial with the smallest angle viewed from the origin was GM in all segments. This indicates that antimicrobials with high similarity and strong asymmetry of similarity against CFPM were GMs, which is consistent with GMs being the antimicrobial with the smallest circle radii in the asymmetric MDS map except for the a2 segment.

In the asymmetric MDS maps, the antimicrobials and antimicrobial groups with higher CRRs and similar antimicrobial effects are displayed closely together. However, when identifying asymmetric similarities such as CRR, it is more accurate to correct the intercentral distance by the radius of their antimicrobials.

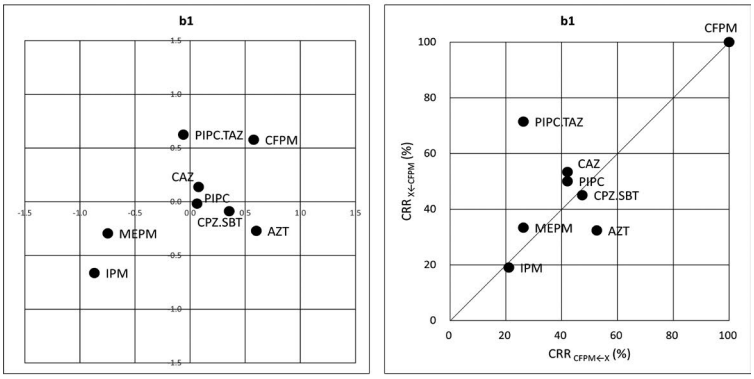
FIGURE 6 Asymmetric multidimensional scaling (MDS) map vs. cross-resistance rate correlation diagram (CRR diagram) *See Table 1 for list of abbreviations



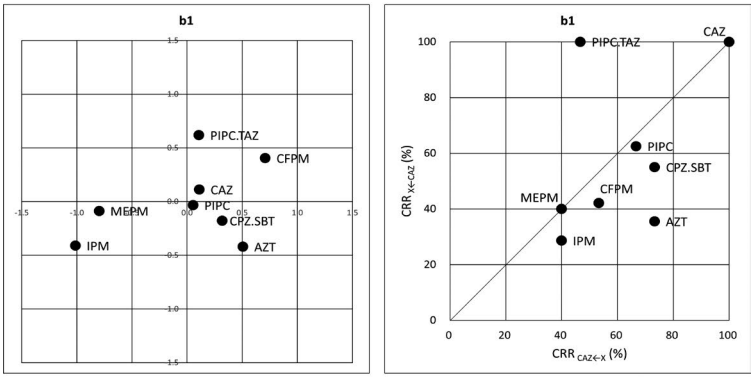
1. Asymmetric MDS map (left) and CRR diagram (right) with cefepime as the base antimicrobial for the 12 antimicrobials belonging to more than 1 group.



2. Asymmetric MDS map (left) and CRR diagram (right) with cefepime as the base antimicrobial for the 8 antimicrobials belonging to more than 1 group.



3. Asymmetric MDS map (left) and CRR diagram (right) with cefepime as the base antimicrobial for the 8 β-lactam antimicrobials.



4. Asymmetric MDS map (left) and CRR diagram (right) with ceftazidime as the base antimicrobial for the 8 β-lactam antimicrobials.

As shown in Figure 5, $m_{B\leftarrow X}$ is inversely correlated with $CRR_{B\leftarrow X}$; however, the circle's radius in the asymmetric MDS map is not solely determined by the association between the selected antimicrobials but is influenced by the association among all antimicrobials. It should therefore be considered that all other antimicrobials affect the distance between antimicrobials corrected by the circle's radius.

4.3 | Cross-resistance rate correlation diagram versus the asymmetric multidimensional scaling map

The arrangement and distance of each antimicrobial on the asymmetric MDS map (Figure 4) based on CRRs could show the similarity and heterogeneity of resistance for each antimicrobial group.

In the CRR diagram, if the base antimicrobial does not change, the coordinates of the antimicrobials do not change when the other antimicrobials that form the diagram are replaced. In the asymmetric MDS, on the contrary, the arrangement of antimicrobials on a map is determined by their similarity to all other antimicrobials. Therefore, if the constituent antimicrobials are changed, the arrangement of the map changes even if the CRRs of the antimicrobials are not changed (Figures 6-1, 6-2, 6-3). Therefore, in the asymmetric MDS map, it is difficult to read the similarities and changes in CRRs for each antimicrobial.

The CRR diagram plots the base antimicrobial in the upper right corner of the square graph plane, so that the other antimicrobials will inevitably be positioned downward to the left in view of the base antimicrobial. Therefore, when the asymmetric MDS map is compared with the CRR diagram, the similarity in their arrangement can increase if the antimicrobials that can capture other antimicrobials within a 0°–90° viewing angle are used as the base antimicrobial. Depending on the selection of the base antimicrobial, the arrangement of antimicrobials in the asymmetric MDS map composed of single-group antimicrobials appears to be consistent with the arrangement in the CRR diagram.

Comparing the CRRs in a3 with those of a2 in the CRR matrix (see Appendix), the CRRs of fluoroquinolones to carbapenems are relatively higher than that of other antimicrobials to carbapenems. Moreover, in the MDS map for the a3 segment (Figure 4.5), the arrangement of the antimicrobial groups appears to have changed significantly from the previous segments. However, if we focus only on the differences in the distances between the groups, we can see that only the distance between carbapenems and fluoroquinolones has changed significantly, whereas the distances among the other groups have not changed significantly from the a2 segment (Figure 4.4), which is a good representation of the change in CRRs in the CRR matrix.

5 | CONCLUSIONS

The CRR diagram illustrates the relationship between the base antimicrobial and each antimicrobial in terms of the CRR value, whereas the asymmetric MDS captures the CRR as a similarity and is an analytical method that illustrates the relationship between all antimicrobials of interest. The scope and underlying techniques of the 2 systems are quite different.

However, the distance between each antimicrobial and other antimicrobials shown in the asymmetric MDS map presented a strong inverse relationship with their CRR against that antimicrobial; moreover, the asymmetric MDS map showed similarities with the plots of the CRR diagram if the constituent antimicrobial groups and base antimicrobials were appropriately selected. Thus, the CRR diagram and asymmetric MDS maps were partially related to each other.

Furthermore, when the asymmetric MDS map is compared with the CRR diagram or other asymmetric MDS, the arrangement needs to be reversed and rotated appropriately. We also found that the antimicrobials should be chosen from the identical group when the similarity between individual antimicrobials is compared and is examined on the asymmetric MDS map.

The combination of CRR diagram and asymmetric MDS analytical techniques allows us to visually and easily understand the landscape and changes in cross-resistance, allowing us to monitor the aspects of resistance of the bacterial flora comprehensively and in detail. In clinical settings, the operational methods considered the most effective are those such as the initial overview of the tendency of cross-resistance among antimicrobial groups by asymmetric MDS analysis followed by the detailed visualization of the relationship between individual antimicrobials using the CRR diagram.

In the future, we would like to explore how to further utilize both methods in clinical settings by analysing the changes in CRRs in various bacterial species over a short period of approximately 6 months, differences between regions and facilities, and variations in outbreaks of resistant bacteria using the combination of the CRR diagram and the asymmetric MDS.

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

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APPENDIX

TABLE A1 CRR matrix for each segment

1. b1 (2013–01 ~ 2014–06)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	37.5 (6/16)	62.5 (10/16)	68.8 (11/16)	50.0 (8/16)	43.8 (7/16)	43.8 (7/16)	81.3 (13/16)	18.8 (3/16)	50.0 (8/16)	31.3 (5/16)	50.0 (8/16)
PIPC/TAZ	85.7 (6/7)	–	100 (7/7)	71.4 (5/7)	71.4 (5/7)	42.9 (3/7)	42.9 (3/7)	85.7 (6/7)	0.0 (0/7)	42.9 (3/7)	28.6 (2/7)	57.1 (4/7)
CAZ	66.7 (10/15)	46.7 (7/15)	–	73.3 (11/15)	53.3 (8/15)	40.0 (6/15)	40.0 (6/15)	73.3 (11/15)	20.0 (3/15)	46.7 (7/15)	40.0 (6/15)	60.0 (9/15)
CPZ/SBT	55.0 (11/20)	25.0 (5/20)	55.0 (11/20)	–	45.0 (9/20)	30.0 (6/20)	35.0 (7/20)	85.0 (17/20)	15.0 (3/20)	40.0 (8/20)	40.0 (8/20)	60.0 (12/20)
CFPM	42.1 (8/19)	26.3 (5/19)	42.1 (8/19)	47.4 (9/19)	–	21.1 (4/19)	26.3 (5/19)	52.6 (10/19)	42.1 (8/19)	68.4 (13/19)	63.2 (12/19)	73.7 (14/19)
IPM	33.3 (7/21)	14.3 (3/21)	28.6 (6/21)	28.6 (6/21)	19.0 (4/21)	–	52.4 (11/21)	33.3 (7/21)	19.0 (4/21)	33.3 (7/21)	28.6 (6/21)	33.3 (7/21)
MEPM	46.7 (7/15)	20.0 (3/15)	40.0 (6/15)	46.7 (7/15)	33.3 (5/15)	73.3 (11/15)	–	40.0 (6/15)	26.7 (4/15)	46.7 (7/15)	46.7 (7/15)	46.7 (7/15)
AZT	41.9 (13/31)	19.4 (6/31)	35.5 (11/31)	54.8 (17/31)	32.3 (10/31)	22.6 (7/31)	19.4 (6/31)	–	16.1 (5/31)	32.3 (10/31)	35.5 (11/31)	48.4 (15/31)
AMK	16.7 (3/18)	0.0 (0/18)	16.7 (3/18)	16.7 (3/18)	44.4 (8/18)	22.2 (4/18)	22.2 (4/18)	27.8 (5/18)	–	94.4 (17/18)	50.0 (9/18)	44.4 (8/18)
GM	19.5 (8/41)	7.3 (3/41)	17.1 (7/41)	19.5 (8/41)	31.7 (13/41)	17.1 (7/41)	17.1 (7/41)	24.4 (10/41)	41.5 (17/41)	–	24.4 (10/41)	26.8 (11/41)
CPFX	17.2 (5/29)	6.9 (2/29)	20.7 (6/29)	27.6 (8/29)	41.4 (12/29)	20.7 (6/29)	24.1 (7/29)	37.9 (11/29)	31.0 (9/29)	34.5 (10/29)	–	86.2 (25/29)
LVFX	27.6 (8/29)	13.8 (4/29)	31.0 (9/29)	41.4 (12/29)	48.3 (14/29)	24.1 (7/29)	24.1 (7/29)	51.7 (15/29)	27.6 (8/29)	37.9 (11/29)	86.2 (25/29)	–
2. b2 (2014–01 ~ 2015–06)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains / total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	58.6 (17/29)	58.6 (17/29)	72.4 (21/29)	55.2 (16/29)	34.5 (10/29)	34.5 (10/29)	75.9 (22/29)	6.9 (2/29)	34.5 (10/29)	20.7 (6/29)	27.6 (8/29)
PIPC/TAZ	94.4 (17/18)	–	88.9 (16/18)	88.9 (16/18)	66.7 (12/18)	38.9 (7/18)	38.9 (7/18)	88.9 (16/18)	0.0 (0/18)	27.8 (5/18)	11.1 (2/18)	16.7 (3/18)
CAZ	81.0 (17/21)	76.2 (16/21)	–	76.2 (16/21)	61.9 (13/21)	33.3 (7/21)	33.3 (7/21)	81.0 (17/21)	9.5 (2/21)	28.6 (6/21)	19.0 (4/21)	23.8 (5/21)
CPZ/SBT	80.8 (21/26)	61.5 (16/26)	61.5 (16/26)	–	57.7 (15/26)	34.6 (9/26)	38.5 (10/26)	92.3 (24/26)	7.7 (2/26)	38.5 (10/26)	15.4 (4/26)	19.2 (5/26)
CFPM	64.0 (16/25)	48.0 (12/25)	52.0 (13/25)	60.0 (15/25)	–	36.0 (9/25)	28.0 (7/25)	68.0 (17/25)	28.0 (7/25)	64.0 (16/25)	40.0 (10/25)	44.0 (11/25)
IPM	29.4 (10/34)	20.6 (7/34)	20.6 (7/34)	26.5 (9/34)	26.5 (9/34)	–	44.1 (15/34)	38.2 (13/34)	14.7 (5/34)	41.2 (14/34)	8.8 (3/34)	11.8 (4/34)
MEPM	52.6 (10/19)	36.8 (7/19)	36.8 (7/19)	52.6 (10/19)	36.8 (7/19)	78.9 (15/19)	–	47.4 (9/19)	15.8 (3/19)	52.6 (10/19)	15.8 (3/19)	15.8 (3/19)
AZT	53.7 (22/41)	39.0 (16/41)	41.5 (17/41)	58.5 (24/41)	41.5 (17/41)	31.7 (13/41)	22.0 (9/41)	–	12.2 (5/41)	39.0 (16/41)	17.1 (7/41)	22.0 (9/41)
AMK	11.8 (2/17)	0.0 (0/17)	11.8 (2/17)	11.8 (2/17)	41.2 (7/17)	29.4 (5/17)	17.6 (3/17)	29.4 (5/17)	–	88.2 (15/17)	47.1 (8/17)	47.1 (8/17)
GM	18.2 (10/55)	9.1 (5/55)	10.9 (6/55)	18.2 (10/55)	29.1 (16/55)	25.5 (14/55)	18.2 (10/55)	29.1 (16/55)	27.3 (15/55)	–	18.2 (10/55)	21.8 (12/55)

(Continues)

TABLE A1 (Continued)

2. b2 (2014–01 ~ 2015–06)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains / total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
CPFX	28.6 (6/21)	9.5 (2/21)	19.0 (4/21)	19.0 (4/21)	47.6 (10/21)	14.3 (3/21)	14.3 (3/21)	33.3 (7/21)	38.1 (8/21)	47.6 (10/21)	–	90.5 (19/21)
LVFX	34.8 (8/23)	13.0 (3/23)	21.7 (5/23)	21.7 (5/23)	47.8 (11/23)	17.4 (4/23)	13.0 (3/23)	39.1 (9/23)	34.8 (8/23)	52.2 (12/23)	82.6 (19/23)	–
3. a1 (2015–07 ~ 2016–12)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	28.6 (2/7)	42.9 (3/7)	42.9 (3/7)	42.9 (3/7)	42.9 (3/7)	28.6 (2/7)	57.1 (4/7)	14.3 (1/7)	28.6 (2/7)	28.6 (2/7)	42.9 (3/7)
PIPC/TAZ	100.0 (2/2)	–	100.0 (2/2)	100.0 (2/2)	100.0 (2/2)	0.0 (0/2)	0.0 (0/2)	100.0 (2/2)	0.0 (0/2)	50.0 (1/2)	50.0 (1/2)	100.0 (2/2)
CAZ	75.0 (3/4)	50.0 (2/4)	–	50.0 (2/4)	75.0 (3/4)	25.0 (1/4)	25.0 (1/4)	75.0 (3/4)	50.0 (2/4)	50.0 (2/4)	50.0 (2/4)	75.0 (3/4)
CPZ/SBT	21.4 (3/14)	14.3 (2/14)	14.3 (2/14)	–	21.4 (3/14)	35.7 (5/14)	28.6 (4/14)	71.4 (10/14)	7.1 (1/14)	21.4 (3/14)	28.6 (4/14)	42.9 (6/14)
CFPM	30.0 (3/10)	20.0 (2/10)	30.0 (3/10)	30.0 (3/10)	–	10.0 (1/10)	10.0 (1/10)	40.0 (4/10)	30.0 (3/10)	80.0 (8/10)	30.0 (3/10)	40.0 (4/10)
IPM	8.6 (3/35)	0.0 (0/35)	2.9 (1/35)	14.3 (5/35)	2.9 (1/35)	–	60.0 (21/35)	17.1 (6/35)	8.6 (3/35)	17.1 (6/35)	5.7 (2/35)	8.6 (3/35)
MEPM	9.5 (2/21)	0.0 (0/21)	4.8 (1/21)	19.0 (4/21)	4.8 (1/21)	100.0 (21/21)	–	28.6 (6/21)	9.5 (2/21)	9.5 (2/21)	4.8 (1/21)	9.5 (2/21)
AZT	15.4 (4/26)	7.7 (2/26)	11.5 (3/26)	38.5 (10/26)	15.4 (4/26)	23.1 (6/26)	23.1 (6/26)	–	7.7 (2/26)	23.1 (6/26)	19.2 (5/26)	26.9 (7/26)
AMK	9.1 (1/11)	0.0 (0/11)	18.2 (2/11)	9.1 (1/11)	27.3 (3/11)	27.3 (3/11)	18.2 (2/11)	18.2 (2/11)	–	90.9 (10/11)	54.5 (6/11)	54.5 (6/11)
GM	4.9 (2/41)	2.4 (1/41)	4.9 (2/41)	7.3 (3/41)	19.5 (8/41)	14.6 (6/41)	4.9 (2/41)	14.6 (6/41)	24.4 (10/41)	–	19.5 (8/41)	19.5 (8/41)
CPFX	11.1 (2/18)	5.6 (1/18)	11.1 (2/18)	22.2 (4/18)	16.7 (3/18)	11.1 (2/18)	5.6 (1/18)	27.8 (5/18)	33.3 (6/18)	44.4 (8/18)	–	88.9 (16/18)
LVFX	14.3 (3/21)	9.5 (2/21)	14.3 (3/21)	28.6 (6/21)	19.0 (4/21)	14.3 (3/21)	9.5 (2/21)	33.3 (7/21)	28.6 (6/21)	38.1 (8/21)	76.2 (16/21)	–
4. a2 (2016–07 ~ 2017–12)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	68.2 (15/22)	68.2 (15/22)	63.6 (14/22)	59.1 (13/22)	36.4 (8/22)	36.4 (8/22)	72.7 (16/22)	4.5 (1/22)	22.7 (5/22)	22.7 (5/22)	27.3 (6/22)
PIPC/TAZ	93.8 (15/16)	–	87.5 (14/16)	81.3 (13/16)	75.0 (12/16)	43.8 (7/16)	37.5 (6/16)	75.0 (12/16)	0.0 (0/16)	25.0 (4/16)	18.8 (3/16)	18.8 (3/16)
CAZ	83.3 (15/18)	77.8 (14/18)	–	66.7 (12/18)	66.7 (12/18)	38.9 (7/18)	33.3 (6/18)	72.2 (13/18)	11.1 (2/18)	27.8 (5/18)	16.7 (3/18)	16.7 (3/18)
CPZ/SBT	53.8 (14/26)	50.0 (13/26)	46.2 (12/26)	–	50.0 (13/26)	46.2 (12/26)	34.6 (9/26)	76.9 (20/26)	3.8 (1/26)	23.1 (6/26)	15.4 (4/26)	19.2 (5/26)

(Continues)

TABLE A1 (Continued)

4. a2 (2016–07 ~ 2017–12)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
CFPM	76.5 (13/17)	70.6 (12/17)	70.6 (12/17)	76.5 (13/17)	–	52.9 (9/17)	47.1 (8/17)	82.4 (14/17)	17.6 (3/17)	35.3 (6/17)	35.3 (6/17)	35.3 (6/17)
IPM	21.6 (8/37)	18.9 (7/37)	18.9 (7/37)	32.4 (12/37)	24.3 (9/37)	–	64.9 (24/37)	29.7 (11/37)	8.1 (3/37)	32.4 (12/37)	18.9 (7/37)	16.2 (6/37)
MEPM	32.0 (8/25)	24.0 (6/25)	24.0 (6/25)	36.0 (9/25)	32.0 (8/25)	96.0 (24/25)	–	36.0 (9/25)	12.0 (3/25)	28.0 (7/25)	16.0 (4/25)	16.0 (4/25)
AZT	35.6 (16/45)	26.7 (12/45)	28.9 (13/45)	44.4 (20/45)	31.1 (14/45)	24.4 (11/45)	20.0 (9/45)	–	4.4 (2/45)	13.3 (6/45)	11.1 (5/45)	13.3 (6/45)
AMK	11.1 (1/9)	0.0 (0/9)	22.2 (2/9)	11.1 (1/9)	33.3 (3/9)	33.3 (3/9)	33.3 (3/9)	22.2 (2/9)	–	88.9 (8/9)	44.4 (4/9)	44.4 (4/9)
GM	13.5 (5/37)	10.8 (4/37)	13.5 (5/37)	16.2 (6/37)	16.2 (6/37)	32.4 (12/37)	18.9 (7/37)	16.2 (6/37)	21.6 (8/37)	–	16.2 (6/37)	16.2 (6/37)
CPFX	20.8 (5/24)	12.5 (3/24)	12.5 (3/24)	16.7 (4/24)	25.0 (6/24)	29.2 (7/24)	16.7 (4/24)	20.8 (5/24)	16.7 (4/24)	25.0 (6/24)	–	75.0 (18/24)
LVFX	31.6 (6/19)	15.8 (3/19)	15.8 (3/19)	26.3 (5/19)	31.6 (6/19)	31.6 (6/19)	21.1 (4/19)	31.6 (6/19)	21.1 (4/19)	31.6 (6/19)	94.7 (18/19)	–

5. a3 (2017–07 ~ 2018–12)												
Base antimicrobial	Cross resistant rate (%) to base antimicrobial (resistant strains/total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	64.7 (11/17)	64.7 (11/17)	64.7 (11/17)	70.6 (12/17)	35.3 (6/17)	29.4 (5/17)	70.6 (12/17)	5.9 (1/17)	29.4 (5/17)	23.5 (4/17)	23.5 (4/17)
PIPC/TAZ	78.6 (11/14)	–	71.4 (10/14)	71.4 (10/14)	64.3 (9/14)	35.7 (5/14)	28.6 (4/14)	71.4 (10/14)	0.0 (0/14)	21.4 (3/14)	14.3 (2/14)	14.3 (2/14)
CAZ	91.7 (11/12)	83.3 (10/12)	–	83.3 (10/12)	75.0 (9/12)	33.3 (4/12)	25.0 (3/12)	75.0 (9/12)	0.0 (0/12)	16.7 (2/12)	8.3 (1/12)	8.3 (1/12)
CPZ/SBT	55.0 (11/20)	50.0 (10/20)	50.0 (10/20)	–	50.0 (10/20)	40.0 (8/20)	30.0 (6/20)	95.0 (19/20)	0.0 (0/20)	25.0 (5/20)	15.0 (3/20)	15.0 (3/20)
CFPM	75.0 (12/16)	56.3 (9/16)	56.3 (9/16)	62.5 (10/16)	–	37.5 (6/16)	31.3 (5/16)	75.0 (12/16)	12.5 (2/16)	56.3 (9/16)	31.3 (5/16)	31.3 (5/16)
IPM	20.0 (6/30)	16.7 (5/30)	13.3 (4/30)	26.7 (8/30)	20.0 (6/30)	–	43.3 (13/30)	33.3 (10/30)	3.3 (1/30)	23.3 (7/30)	20.0 (6/30)	23.3 (7/30)
MEPM	38.5 (5/13)	30.8 (4/13)	23.1 (3/13)	46.2 (6/13)	38.5 (5/13)	100.0 (13/13)	–	53.8 (7/13)	0.0 (0/13)	38.5 (5/13)	30.8 (4/13)	30.8 (4/13)
AZT	26.7 (12/45)	22.2 (10/45)	20.0 (9/45)	42.2 (19/45)	26.7 (12/45)	22.2 (10/45)	15.6 (7/45)	–	0.0 (0/45)	20.0 (9/45)	13.3 (6/45)	17.8 (8/45)
AMK	20.0 (1/5)	0.0 (0/5)	0.0 (0/5)	0.0 (0/5)	40.0 (2/5)	20.0 (1/5)	0.0 (0/5)	0.0 (0/5)	–	100.0 (5/5)	40.0 (2/5)	40.0 (2/5)
GM	11.1 (5/45)	6.7 (3/45)	4.4 (2/45)	11.1 (5/45)	20.0 (9/45)	15.6 (7/45)	11.1 (5/45)	20.0 (9/45)	11.1 (5/45)	–	13.3 (6/45)	13.3 (6/45)
CPFX	20.0 (4/20)	10.0 (2/20)	5.0 (1/20)	15.0 (3/20)	25.0 (5/20)	30.0 (6/20)	20.0 (4/20)	30.0 (6/20)	10.0 (2/20)	30.0 (6/20)	–	95.0 (19/20)
LVFX	18.2 (4/22)	9.1 (2/22)	4.5 (1/22)	13.6 (3/22)	22.7 (5/22)	31.8 (7/22)	18.2 (4/22)	36.4 (8/22)	9.1 (2/22)	27.3 (6/22)	86.4 (19/22)	–

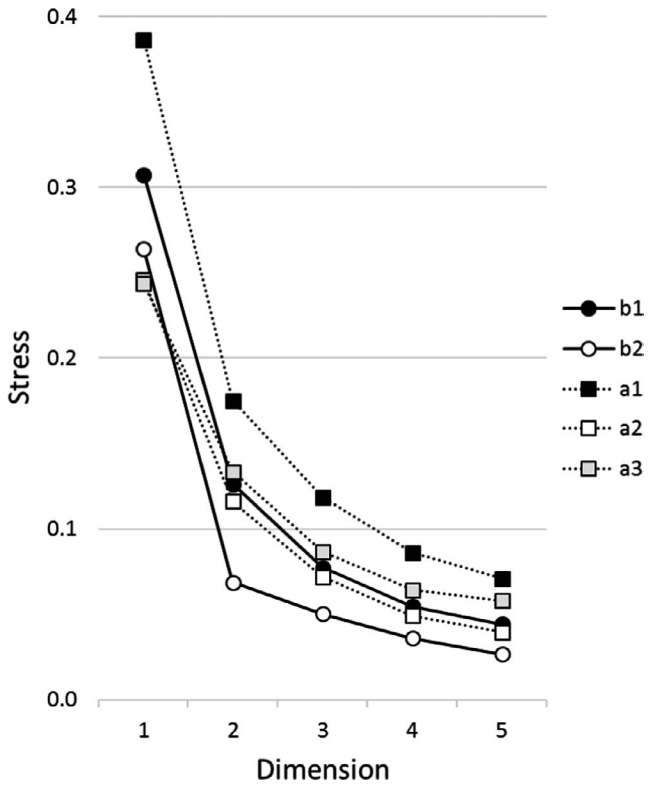

FIGURE A1 Scree plot of stress values of 1-5d MDS distributions for each segment data