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# Drug Susceptibility of Isolates from Severe Postoperative Intraperitoneal Infections Causing Multiple Organ Failure

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**Abstract**

***Purpose.*** To select the most appropriate antibiotic regimens for life-threatening postoperative infections, we obtained isolates from patients with severe postoperative infections over a 12-year-period, and examined their drug susceptibility.

***Methods.*** The subjects of this study were 55 patients with multiple organ failure (MOF) caused by postoperative infection.

***Results.*** All strains of Methicillin-resistant *Staphylococcus aureus* (MRSA) were susceptible to Vancomycin (VCM) and Teicoplanin (TEIC). Only 0.3% of all the *Pseudomonas aeruginosa* strains were resistant to Imipenem (IPM), but 53.6% of the strains from the severe infections were resistant to IPM. On the other hand, there were few *P. aeruginosa* strains resistant to Meropenem (MEPM), Ceftazidime (CAZ), Ciprofloxacin (CPFX), and Pazufloxacin (PZFX), even among strains isolated from severe infections. The resistant rate of *Bacteroides fragilis* to Clindamycin (CLDM) was 35.9%, but there were strains resistant to IPM and Panipenem.

***Conclusion.*** These findings suggest that VCM or TEIC are most appropriate for severe abdominal abscess caused by MRSA, whereas MEPM, CAZ, CPFX, and PZFX are more effective against *P. aeruginosa* infections. The only antibiotic effective against *B. fragilis* infections in this study was IPM.

**Key words** Postoperative infection · Severe intraperitoneal infection · Methicillin-resistant *Staphylococcus aureus* · Imipenem

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## Introduction

With the emergence of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections in hospitals in Japan, the protocols for administering antibiotics have been reviewed. As a general rule, antibiotics with a narrow spectrum are given to prevent postoperative infections, and previously administered antibiotics are given whenever possible. Furthermore, antibiotics should not be given for a localized colonization if there are no signs of systemic infection. In this way, MRSA and other multidrug-resistant infections caused by microbial substitution are being prevented, and the frequency of their isolation is decreasing.[1,2] However, for surgical patients with prolonged and aggravated intraperitoneal infections caused by digestive tract suture failure, treatment with several different antibiotics is necessary. Thus, the problem of multidrug-resistant bacterial infections persists. The antibiotics used to treat severe postoperative infections are selected based on drug susceptibility to the isolates. However, because drug susceptibility testing requires at least 3–4 days, if patients with severe infection are treated, empiric therapy must be performed by predicting the isolated strains and their susceptibility. Therefore, in this study we examined the drug susceptibility of MRSA, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* based on the same perioperative antibiotic protocols used in a teaching ward during the last 12.5 years, to help select the most effective antibiotics when performing empiric therapy for severe postoperative infections.

## Subjects and Methods

During the 12.5 years between March 1990 and August 2002, 4800 patients underwent digestive tract surgery at our hospital. Severe postoperative infections resulting in multiple organ failure (MOF) developed in 55 of

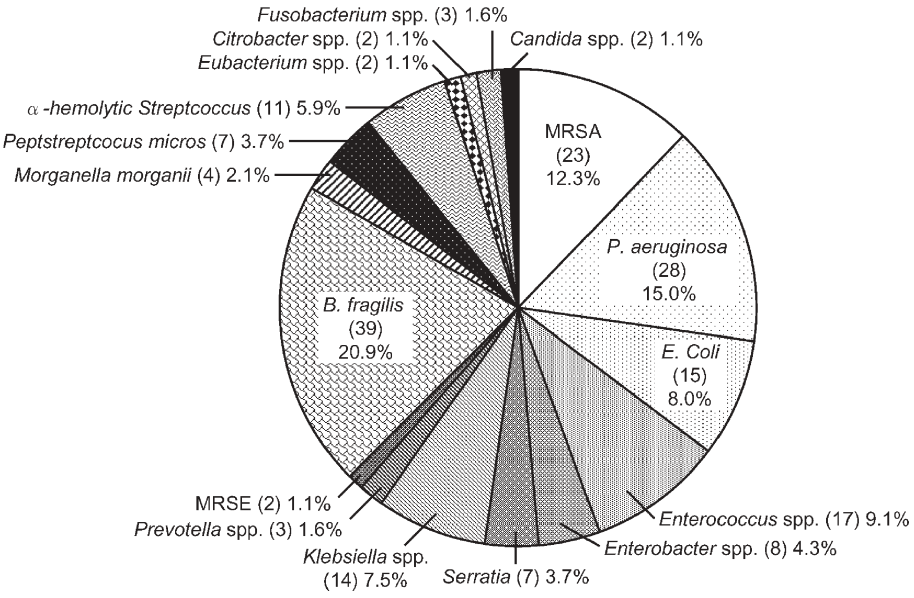


**Fig. 1.** Causative organisms (55 patients, 187 strains). Causative organisms of severe and persistent postoperative infections in the 55 patients. *Bacteroides fragilis*, *Pseudomonas aeruginosa*, and Methicillin-resistant *Staphylococcus aureus* were most prevalent

**Table 1.** Underlying diseases

| | |
|---|---|
| Gastric cancer | 21 |
| Pancreatic cancer | 6 |
| Liver cancer | 3 |
| Perforation of upper GI | 3 |
| Perforation of small intestine | 18 |
| Perforation of colon | 4 |

Most of the patients underwent surgery for gastric cancer or small bowel perforation
GI, gastrointestinal tract

**Table 2.** Infectious sites (including overlapping cases)

| | |
|---|---|
| Abdominal abscess (including 49 with anastomotic leakage) | 53 |
| MRSA enterocolitis | 1 |
| Bacterial translocation | 1 |

Of the 55 patients with infections, 53 had a peritoneal abscess, 49 of which were attributed to suture failure
MRSA, Methicillin-resistant *Staphylococcus aureus*

these patients, who were the subjects of this study. The underlying reasons for surgery were, primarily, stomach cancers and perforated small bowel (Table 1). We changed our protocols for perioperative antibiotic use in March 1990. For upper digestive tract surgery, we gave first-generation cephams (Cefazolin; CEZ) as postoperative prophylaxis and second-generation cephams as first line therapeutic drugs for a postoperative infection. If the postoperative infection could not be controlled, we gave fourth-generation cephams and if the infection persisted, we gave carbapenem.[2] For lower digestive tract surgery, we gave second-generation cephams (Cefotiam; CTM) as postoperative prophylaxis, and second-generation cephams (Cefmetazole; CMZ, Flomoxef; FMOX) as first-line therapeutic drugs for a postoperative infection. If the postoperative infection could not be controlled, we gave carbapenem. The present study examines the sites of infection, the isolated bacteria, and the susceptibility of principal isolates to different drugs. When different bacteria were isolated simultaneously, all strains were collected. Drug susceptibility, defined as the minimum inhibitory concentration (MIC) was measured in accordance with the standard method of the Japanese Society of Chemotherapy, and the break point was in compliance with The National Committee for Clinical Laboratory Standards (NCCLS). Statistical analysis was done by the chi-square test and significance was considered at $P < 0.001$.

## Results

The infection manifested as abdominal abscess in 53 of the 55 patients, 49 of whom had accompanying anastomotic leakage of the digestive tract (Table 2). The predominant isolates were MRSA (12.3%), *P. aeruginosa* (15.0%), and *B. fragilis* (20.9%) (Fig. 1). With respect to MRSA drug susceptibility, there were no strains resistant to Vancomycin (VCM) or Teicoplanin (TEIC), but 13.0% were resistant to Arbekacin (ABK) (Table 3). With respect to *P. aeruginosa* drug susceptibility, 53.6% of the strains (15/28) showed resistance to both Imipenem (IPM) and Panipenem (PAPM) carbapenems. All of the IPM-resistant strains were resistant to PAPM. There was one strain (3.6%) resistant to

Meropenem (MEPM), and this strain also showed resistance to IPM and PAPM. All except one of the IPM- and PAPM-resistant strains were susceptible to MEPM (Table 4). With respect to the cephams, there were two strains (7.1%; 2/28) resistant to Ceftazidime (CAZ), both of which were also resistant to IPM and PAPM. No strains were resistant to the New Quinolone drugs, Ciprofloxacin (CPFX) and Pazufloxacin (PZFX). However, in terms of drug susceptibility to *B. fragilis*, although there were no strains resistant to IPM or PAPM, 5.1% (2/39) showed resistance to MEPM and 35.9% (14/39) showed resistance to Clindamycin (CLDM) (Table 5).

## Discussion

In Japan, the protocols for the use of antibiotics in surgery were revised following the emergence of MRSA infections. This has resulted in a decreasing incidence of multidrug-resistant strains of bacteria, such as MRSA.[1,2] The development of multidrug-resistant bacterial strains is attributed to the narrow antibacterial spectrum for antibiotics used to prevent postoperative infection, the use of previous drugs, and the fact that antibiotics should not be given to patients with a postoperative infection unaccompanied by signs of systemic infection. As a result, the selection of microbial-substitution-induced multidrug-resistant strains such as MRSA is being prevented, and multidrug-resistant strain infections such as postoperative MRSA are becoming less common.[2] It is well known that multidrug-resistant strains are predominant in bacteria isolated from patients with severe infection. This is because many severe infections after digestive tract surgery de-

**Table 3.** Susceptibility of MRSA (23 strains from 55 patients)

| | S | I | R |
|---|---|---|---|
| VCM | 100% | 0 | 0 |
| TEIC | 100% | 0 | 0 |
| ABK | 86.9% | 0 | 13.1% |

No isolated MRSA strains were resistant to Vancomycin (VCM) or Teicoplanin (TEIC), but 13.1% were resistant to Arbekacin (ABK)

**Table 5.** Drug susceptibility of *Bacteroides fragilis* (39 strains from 55 patients)

| | Drug | | | |
|---|---|---|---|---|
| MIC (ng/ml) | IPM | PAPM | MEPM | CLDM |
| ≤256 | | | | 5 |
| 128 | | | | 6 |
| 64 | | | | 3 |
| 32 | | | 2 | |
| 16 | | | | |
| 8 | | 1 | | |
| 4 | | 5 | 1 | |
| 2 | 6 | 5 | 5 | 2 |
| 1 | 7 | 2 | 2 | 8 |
| 0.5 | 3 | 0 | 2 | 1 |
| 0.25 | 17 | 13 | 18 | 5 |
| 0.12 | 4 | 10 | 10 | 9 |
| 0.06 | 2 | 3 | | |
| Resistant strains | 0 | 0 | 5.1% (2/39) | 35.9% (14/39) |

No isolated *B. fragilis* strains were resistant to Imipenem (IPM) or Panipenem (PAPM), but 5.1% and 35.9% were resistant to Meropenem (MEPM) and Clindamycin (CLDM), respectively
MIC, minimum inhibitory concentration

**Table 4.** Drug susceptibility of *Pseudomonas aeruginosa* (28 strains from 55 patients)

| | Drug | | | | | |
|---|---|---|---|---|---|---|
| MIC (ng/ml) | IPM | PAPM | MEPM | CAZ | CPFX | PZFX |
| 64 | | | | 2 | | |
| 32 | 6 | 6 | | | | |
| 16 | 9 | 9 | 1 | 1 | | |
| 8 | 6 | 5 | | 1 | | |
| 4 | 1 | 2 | 3 | 5 | | |
| 2 | 5 | 5 | | 8 | | 2 |
| 1 | 1 | 1 | 8 | 11 | | 3 |
| 0.5 | | | 11 | | 1 | 15 |
| 0.25 | | | 5 | | 5 | 8 |
| 0.12 | | | | | 22 | |
| Resistant strains | 53.6% (15/28) | 53.6% (15/28) | 3.6% (1/28) | 7.1% (2/28) | 0 | 0 |

Of the isolated *P. aeruginosa* strains, 53.6% were resistant to Imipenem (IPM) and Panipenem (PAPM), and 3.6% and 7.1% were resistant to Meropenem (MEPM) and Ceftazidime (CAZ), respectively. No strains were resistant to Ciprofloxacin (CPFX) or Pazufloxacin (PZFX)
MIC, minimum inhibitory concentration

velop in patients who have undergone several unsuccessful attempts at surgical drainage. These patients usually have a long treatment course and are given various antibiotics until the infection becomes uncontrollable. Consequently, antibiotic selection for severe infections is often difficult. When selecting an antibiotic, the results of drug sensitivity testing are vitally important, which usually requires 3–4 days, so during that time empiric therapy must be given. If the antibiotic regimen is the same in any department, it is relatively easy to predict the etiological agent and its susceptibility based on the accumulation of data of isolate susceptibility in previous patients. Based on this reasoning, we retrospectively examined patients with severe infection treated in our hospital during the last 12.5 years to evaluate the strains isolated and their drug susceptibility. The MRSA isolated from these subjects showed good susceptibility to VCM and TEIC, but 13.0% showed resistance to ABK; however, the ABK-resistant strains were isolated from patients during the early period when ABK was used in abundance. Strains isolated more recently showed good susceptibility. Consequently, antibiotic therapy for MRSA infection should be adequately dealt with by existing anti-MRSA drugs. Among the antibiotic regimens, we designated IPM as the third choice of drug to treat infection. Therefore, in *P. aeruginosa* isolated from mild postoperative infections, there were no IPM-resistant strains seen, but in *P. aeruginosa* isolated from severe infections, a high 53.6% were resistant to IPM. These IPM-resistant *P. aeruginosa* strains were also resistant to PAPM, but with respect to the same carbapenem antibiotics, only 3.6% were resistant to MEPM, 7.1% were resistant to CAZ, and more were resistant to CPFX and PZFX. In general, carbapenems and many β-lactam antibiotics act on penicillin-binding proteins (PBPs), which synthesize the peptidoglycan that forms the cell wall, and inhibit peptidoglycan synthesis. The reason *P. aeruginosa* becomes less resistant to MEPM than to IPM or PAPM is that MEPM has a higher affinity to the PBPs, PBP2 and PBP3, than other carbapenems.[3,4] Furthermore, *P. aeruginosa* has strong outer membrane interception against substance penetration, even among the Gram-negative bacteria, which is assumed to be one of the factors of natural tolerance against many drugs.[5,6] Even with drugs that can penetrate the outer membrane, there are other factors, such as deactivation by intracellular inactivated enzymes, and extracellular pumping out by an elimination pump when the rate of penetration is slow.[7] Meropenem is thought to have a rate of penetration twice as fast as that of carbapenems.[8] This is because IPM- and PAPM-resistant strains lack an outer membrane protein (Opr) D, which forms outer membrane penetration pores, preventing these drugs from penetrating the outer membrane. However, MEPM is not influenced greatly by this, so is expected to be effective.[9] Of the IPM-resistant *P. aeruginosa* strains, susceptibility to CAZ among the OprD2, OprC, and OprE1 deficiency strains is maintained at a low MIC of 1.56 μg/ml.[10] Therefore, it is anticipated the antibacterial activity of CAZ against IPM-resistant *P. aeruginosa* will be maintained.[11,12] According to recent reports, the new quinolones, such as CPFX and PZFX, have a MIC of no more than 0.78 μg/ml against all deficient strains.[10] It has also been reported that the susceptibility of IPM-resistant *P. aeruginosa* to CPFX is excellent,[13] in agreement with our findings.

With respect to *B. fragilis* drug susceptibility, no strains were resistant to IPM and PAPM, but 5.1% showed resistance to MEPM. The MIC of *B. fragilis* increases in an acidic environment. In fact, the MIC of 5 μg/ml at pH 7.1 increases to at least 16 μg/ml, which is the NCCLS breakpoint at pH 6.8, then at pH 5.8 it rises to at least 40 μg/ml. Meropenem is not affected in this way.[14] The fact that IPM has a very high affinity with PBP,[10] and high resistance against β-lactamase,[15] suggests that the susceptibility of *B. fragilis* to IPM would be good. On the other hand, there was a high percentage (35.9) of *B. fragilis* strains resistant to CLDM in this study. In Japan, CPFX was approved in 2001 and PZFX was approved in 2003, opening the way for treating IPM-resistant *P. aeruginosa* infections and IPM- and cepham-resistant Gram-negative bacillus infections, but their antibacterial activity against *B. fragilis* is weak. In the West, Metronidazole (MTN) is used to treat infections caused by *B. fragilis* because there are virtually no *B. fragilis* strains resistant to MTN.[16,17] However, in Japan intravenous MTN is not yet approved and *B. fragilis* susceptibility to CLDM is poor, so the difficulty in selecting drugs to treat severe *B. fragilis* infections is a major issue. Therefore, it is expected that mixed infections caused by IPM-resistant *P. aeruginosa* and *B. fragilis* will have to be treated by a combination of new quinolones or CAZ and IPM or PAPM. To avoid this, if New Quinolones are given as the first line of treatment for postoperative infections, we may delay the emergence of IPM-resistant *P. aeruginosa*, and effectively mitigate the chances of a mixed infection caused by IPM-resistant *P. aeruginosa* and *B. fragilis*. Even so, if a mixed infection caused by *P. aeruginosa* and *B. fragilis* developed, concomitant antibiotic therapy would have to be given.

We have provided digestive tract perioperative antibiotic therapy for 12.5 years using virtually the same regimen. Despite the many reports of the problematic emergence of resistant strains caused by continued use of the same antibiotic, in our regiment, CEZ is given to prevent infections in upper digestive tract surgery, and CTM is given to prevent infections in lower digestive tract surgery. If infection does develop, we give second-

generation cephams, and if the infection can then still not be controlled, we give fourth-generation cephams. Only if the infection persists do we give carbapenem antibiotics.[1] Thus, carbapenems constitute no more than 20% of the total usage of all antibiotics.[2] Carbapenem-resistant *P. aeruginosa* accounted for at least half of the severe persistent infections in this series, but examination of all the postoperative infections during the study period revealed 249 strains of *P. aeruginosa* isolated from 731 patients with postoperative infections among 4800 patients who underwent surgery during this period. Only 0.60% (15/249) were caused by carbapenem-resistant *P. aeruginosa*, which means that only a minuscule 0.31% were isolated from the study subjects, which affirms the antibiotic regimen we select perioperatively.

In conclusion, we examined the drug susceptibility of isolates in severe cases of infection after digestive tract surgery over a 12.5-year period based on the same perioperative antibiotic regimen. Although 13.0% of the MRSA infections were resistant to ABK during the early period of this study, there were no MRSA strains resistant to VCM and TEIC. Moreover, although 53.6% of the *P. aeruginosa* strains were resistant to IPM, there were few strains resistant to MEPM, CAZ, and CPFX and PZFX. Finally, there were no IPM-resistant strains of *B. fragilis*, but resistance was building to CLDM and therefore, the selection of a therapeutic agent was limited.

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