Ceftolozane/tazobactam and imipenem/relebactam cross-susceptibility among clinical isolates of
Pseudomonas aeruginosa from patients with respiratory tract infections in ICU and non-ICU
wards – SMART United States 2017-2019

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Summary of key points:

Antimicrobial resistance among *P. aeruginosa* from respiratory tract infections is common, especially in ICUs. A substantial proportion of isolates that were ceftolozane/tazobactam-nonsusceptible were imipenem/relebactam-susceptible and vice versa. Both agents could provide important treatment options and should be considered for testing.
Abstract

Background: Carbapenem-nonsusceptible and multidrug-resistant (MDR) *P. aeruginosa*, which are more common in patients with lower respiratory tract infections (LRTIs) and in patients in ICUs, pose difficult treatment challenges and may require new therapeutic options. Two β-lactam/β-lactamase-inhibitor combinations, ceftolozane/tazobactam (C/T) and imipenem/relebactam (IMI/REL), are approved for treatment of hospital-acquired/ventilator-associated bacterial pneumonia.

Methods: CLSI-defined broth microdilution methodology was used to determine MICs against *P. aeruginosa* isolates collected from patients with LRTIs in ICU (n=720) and non-ICU wards (n=914) at 26 United States hospitals in 2017-2019 as part of the SMART surveillance program.

Results: Susceptibility to commonly used β-lactams including carbapenems was 5-9 percentage points lower and MDR rates 7 percentage points higher among isolates from patients in ICUs than non-ICU wards (p<0.05). C/T and IMI/REL maintained activity against 94.0% and 90.8% of ICU isolates, respectively, while susceptibility to all comparators except amikacin (96.0%) was 63-76%. C/T and IMI/REL inhibited 83.1% and 68.1% of meropenem-nonsusceptible (n=207) and 71.4% and 65.7% of MDR ICU isolates (n=140), respectively. Among all ICU isolates, only 2.5% were nonsusceptible to both C/T and IMI/REL, while 6.7% were susceptible to C/T but not to IMI/REL, and 3.5% were susceptible to IMI/REL but not to C/T.

Conclusions: These data suggest that susceptibility to both C/T and IMI/REL should be considered for testing at hospitals, as both agents could provide important new options for treating patients with LRTIs, especially in ICUs where collected isolates showed substantially reduced susceptibilities to commonly used β-lactams.

Key words: ceftolozane/tazobactam, imipenem/relebactam, *Pseudomonas aeruginosa*, respiratory tract infection, ICU
Introduction

Carbapenem-resistant *P. aeruginosa* is listed as a “Priority 1: Critical” pathogen on the Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics that was compiled by the World Health Organization in 2017 [1]. Isolates with this phenotype and other resistant subsets of *P. aeruginosa*, including multidrug-resistant isolates, have been found more commonly among patients in ICUs than other wards [2-7]. Resistant phenotypes of *P. aeruginosa* have also been found more commonly among respiratory tract isolates compared to intraabdominal, urinary tract, and skin/wound isolates [3, 7-12]. These problematic pathogens require new treatment options, especially for patients in ICUs and those with respiratory tract infections.

The cephalosporin ceftolozane was developed specifically to have enhanced antibacterial activity against *P. aeruginosa*. Ceftolozane is less susceptible to hydrolysis by AmpC β-lactamases (PDC), is a weak substrate for efflux pumps, and is not affected by OprD loss [13, 14]. The β-lactamase inhibitor tazobactam inhibits most class A and some class C β-lactamases (e.g. DHA) and was combined with ceftolozane to broaden the gram-negative spectrum of coverage to many ESBL-producing Enterobacterales, yet doesn’t contribute to the antipseudomonal activity of ceftolozane. Ceftolozane/tazobactam (C/T) retains activity against the large majority of isolates resistant to carbapenems and other commonly used antipseudomonal β-lactams [15]. However, when isolates become resistant to C/T, treatment options are extremely limited. Imipenem/relebactam (IMI/REL) is a carbapenem (IMI) combined with cilastatin and a novel β-lactamase inhibitor (REL), active against class A and C β-lactamases, that has been shown to restore imipenem susceptibility among Enterobacterales and *P. aeruginosa* [16]. Both agents are approved for the treatment of hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) [17, 18].

Resistance in *P. aeruginosa* isolates can be complex and is often mediated by multiple chromosomally-encoded enzymatic and non-enzymatic mechanisms as well as acquired enzymes. Both C/T and IMI/REL are active against the majority of *P. aeruginosa* isolates with derepressed chromosomally-encoded AmpC (PDC) and porin defects or upregulated efflux transport [13, 14, 16, ...
However, C/T and IMI/REL are affected by mechanisms of resistance in various ways that can permit *P. aeruginosa* isolates to be nonsusceptible to one agent, while still remaining susceptible to the other agents. For example, C/T is not active against *P. aeruginosa* carrying metallo-β-lactamases (MBLs), KPCs, most isolates carrying ESBLs (e.g., PER, VEB), PDC subtypes with mutations that increase hydrolysis of ceftolozane and ceftazidime, or isolates producing PDC at very high levels [13, 14, 16, 19-24]. IMI/REL is not active against *P. aeruginosa* carrying MBLs or some GES subtypes, or isolates with porin defects that also hyperproduce AmpC at very high levels [16, 19, 20]. Although published data is lacking, IMI/REL is not expected to show activity against *P. aeruginosa* carrying OXA-type β-lactamases, some of which may be susceptible to C/T [25]; however, it should be noted that several OXA-type enzymes with extended spectrum activity (e.g. OXA-14) have been reported to confer resistance to C/T [22, 26].

Because of differences in the susceptibility profiles of the two agents, both may have a role in the treatment of resistant *P. aeruginosa* isolates. We compared the activity of C/T and IMI/REL against recent clinical isolates of *P. aeruginosa* collected in the United States as part of the global Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program. Because of the high prevalence and increased resistance of *P. aeruginosa* among isolates from lower respiratory tract infections, we focused on this infection source, and because of higher resistance among isolates from ICU patients, we compared isolates from patients in ICU and non-ICU-wards.

**Materials and Methods**

**Bacterial isolates**

Twenty-six clinical laboratories in 18 states (California, Colorado, Florida, Georgia, Illinois, Indiana, Kentucky, Michigan, Minnesota, Nebraska, New York, North Carolina, Ohio, Pennsylvania, Texas, Utah, Washington, and Wisconsin), covering eight of the nine United States Census Bureau Divisions (all except New England), each collected up to 100 consecutive clinically relevant isolates of aerobic or facultative gram-negative bacilli from patients with lower respiratory tract infections per year. Only one isolate per species per patient per year was accepted into the study. All isolates were
transported to a central laboratory (IHMA, Schaumburg, IL, USA), where they were re-identified using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA, USA).

**Antimicrobial susceptibility testing**

Antimicrobial susceptibility testing was performed following the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method [27, 28], using custom-made dehydrated broth microdilution panels manufactured by TREK Diagnostic Systems in 2017 (Thermo Fisher Scientific, Waltham, MA, USA) and frozen broth microdilution panels prepared at IHMA in 2018 and 2019. Relebactam and tazobactam were tested at a fixed concentration of 4 µg/mL, in combination with doubling-dilutions of imipenem and ceftolozane, respectively. Avibactam was obtained from BioChemPartner (www.biocompartner.com) and tested at a fixed concentration of 4 µg/mL combined with ceftazidime, starting in 2018.

Minimum inhibitory concentrations (MICs) were interpreted as susceptible, intermediate, or resistant using 2021 CLSI breakpoints [28]. MDR isolates were defined phenotypically as those isolates resistant to three or more of the following seven sentinel antimicrobial agents: amikacin, aztreonam, cefepime, levofloxacin, colistin, imipenem, and piperacillin/tazobactam. Pan-β-lactam-nonsusceptible isolates were defined as nonsusceptible (with intermediate or resistant MICs) to the following tested β-lactams (cefepime, ceftazidime, aztreonam, piperacillin/tazobactam, imipenem, meropenem). Difficult-to-treat resistance (DTR) was defined as isolates testing as nonsusceptible to all tested β-lactams (excluding C/T, IMI/REL, and ceftazidime/avibactam) and fluoroquinolones (ciprofloxacin [only tested in 2017-2018] and levofloxacin) [29].

**Statistical analysis**

Differences in proportions of susceptible and nonsusceptible phenotypes between isolates collected from patients in ICU and non-ICU wards were assessed for statistical significance with Fisher’s exact test using XLSTAT version 2020.1.3. A p value <0.05 was considered statistically significant.
Results

A total of 2578 and 2456 gram-negative pathogens were collected from patients with LRTI in ICU and non-ICU wards, respectively. *P. aeruginosa* was the most common species with 720 (27.9%) and 914 (37.2%) collected isolates, respectively, followed by *Klebsiella pneumoniae* (338 [13.1%] and 241 [9.8%], respectively) and *Escherichia coli* (291 [11.3%] and 225 [9.2%], respectively).

Antimicrobial susceptibility was generally lower among *P. aeruginosa* isolates from patients in ICU compared to non-ICU wards, with susceptibility to commonly used β-lactams 5-9 percentage points lower in ICU than non-ICU wards (p<0.05) (Figure 1). The differences were smaller (3 percentage points or less) for C/T (p=0.02), IMI/REL (p=0.049), and amikacin (p=0.43). These three agents maintained susceptibility rates of >90% among isolates from patients in both ICU and non-ICU wards. Susceptibility to all other comparators was 63-76% in ICUs. The proportion of nonsusceptible phenotypes among *P. aeruginosa* isolates collected in ICU and non-ICU wards is shown ranked by prevalence in Figure 2. C/T-nonsusceptible and IMI/REL-nonsusceptible isolates were less common than MDR, pan-β-lactam-nonsusceptible, and DTR isolates in both ICU and non-ICU wards. The latter three subsets were significantly more prevalent among ICU isolates (10.0-19.4%) than non-ICU isolates (6.1-12.5%, p<0.01).

Table 1 shows the activity of C/T, IMI/REL, and comparators against isolates with the studied resistance phenotypes. Susceptibility in general was lower in ICU than non-ICU wards; however, statistically significant differences were not common and found mostly for ceftazidime and aztreonam. C/T remained active against 77-87% of ICU isolates that were nonsusceptible to at least one commonly used β-lactam and against 61-71% of MDR, pan-β-lactam-nonsusceptible, and DTR isolates from ICU patients. The activity of IMI/REL was 1 to 15 percentage points lower than C/T among the studied nonsusceptible subsets collected from ICU patients; however, it maintained activity against 58.1% and 59.4% of C/T-nonsusceptible ICU and non-ICU isolates, respectively, while the tested carbapenems were active against 19-31% of C/T-NS isolates. Similarly, C/T maintained activity against 72.7% and 78.0% of IMI/REL-nonsusceptible ICU and non-ICU isolates,
respectively, and the tested cephalosporins and piperacillin/tazobactam were active against 21-54\% of isolates.

More detailed cross-susceptibility analyses showed that among the 720 isolates collected from patients in ICUs, only 2.5\% were nonsusceptible to both C/T and IMI/REL, while a larger proportion (10.1\%) was susceptible to either C/T or IMI/REL but not to the other agent (C/T-susceptible IMI/REL-nonsusceptible, 6.7\%; IMI/REL-susceptible C/T nonsusceptible, 3.5\%) (Table 2a). Among non-ICU isolates, the percentages of isolates nonsusceptible to both agents (1.4\%) or to one agent but not the other (7.1\%) were slightly smaller (Table 2b). When limiting this analysis to only MDR isolates (Table 3a and b), the proportions of isolates that were susceptible to C/T or IMI/REL but not to the other agent were more pronounced, especially among ICU isolates (37.1\%); 87.1\% of MDR ICU isolates were susceptible to either C/T or IMI/REL. Similar results were found when limiting this analysis to pan-\(\beta\)-lactam-nonsusceptible isolates (Supplemental Table S1 a and b) and DTR isolates (Supplemental Table S2 a and b): the proportion of isolates that were susceptible to C/T or IMI/REL but not to the other agent was 37.8\% and 40.3\% among pan-\(\beta\)-lactam-nonsusceptible and DTR ICU isolates, respectively; 80.0\% of pan-\(\beta\)-lactam-nonsusceptible and 77.8\% of DTR ICU isolates were susceptible to either C/T or IMI/REL.

Because susceptibility data for ceftazidime/avibactam (CZA) were only available for isolates collected in 2018 and 2019, analyses comparing the activity of CZA to the other tested agents were restricted to these years and are shown in Supplemental Table S3. Among the three newer \(\beta\)-lactam/\(\beta\)-lactamase inhibitor agents, C/T generally showed the highest activity against \textit{P. aeruginosa} collected in the ICU setting among all isolates and the nonsusceptible phenotypes tested. CZA also showed appreciable activity among isolates with the nonsusceptible phenotypes listed and was generally comparable to IMI/REL, however, both agents demonstrated activity that was 5-19 percentage points lower than observed for C/T among ICU isolates. The differences in activity were more prominent among isolates with more resistant phenotypes such as MDR, pan-\(\beta\)-lactam-nonsusceptible, and DTR subsets. In general, percentages of susceptibility to C/T and CZA were similar among isolates from non-ICU settings. CZA retained activity against C/T-nonsusceptible isolates from both the ICU
(35.0%) and non-ICU (42.1%) settings, but susceptibility was approximately 25 percentage points lower than to IMI/REL in this scenario. Similarly, CZA retained activity against 66.7% and 79.4% of ICU and non-ICU isolates that were IMI/REL-nonsusceptible, but these values were 14 percentage points lower than observed for C/T among ICU isolates. Both C/T and IMI/REL maintained 42-63% activity against CZA-resistant isolates. It should be noted that many of these comparisons should be interpreted with caution due to small sample sizes, especially for C/T-nonsusceptible isolates.

Discussion

Prior studies, including reports from both the SMART and SENTRY programs, have reported higher resistance among isolates from patients in ICUs than non-ICU wards [4, 5, 7] as well as among LRTI isolates [7-12]. In the current study, we were able to expand these findings as we focused on LRTI isolates from US patients and compared the two ward types. In contrast to the study by McCann et al., which did not see a higher rate of carbapenem-nonsusceptible P. aeruginosa isolates among respiratory isolates from patients in ICUs compared to non-ICU wards [7], we found that the ICU/non-ICU pattern persisted among LRTI isolates, with antimicrobial susceptibility among LRTI isolates significantly reduced for ICU isolates compared to those from non-ICU wards. For example, susceptibility to ceftazidime was 72.6% and 81.8%, respectively, and that to meropenem was 71.3% and 77.2%, respectively (p<0.05). The susceptibility among ICU isolates was generally lower than that reported by Sader et al. among P. aeruginosa isolates collected from patients with pneumonia hospitalized in US ICUs (81.3% and 73.9% susceptible to ceftazidime and meropenem, respectively) [30]. These differences may reflect participation in the two studies of different hospitals in different regions of the United States as well as the fact that Sader et al. analyzed isolates collected from 2015-2017, while the current SMART study describes isolates collected from 2017-2019. A study by Asempa et al. of isolates collected in 2017-2018 showed susceptibility rates among respiratory isolates from patients in US ICUs that were more similar to those found in the current study (74.6% and 69.1% susceptible to ceftazidime and meropenem, respectively) [31]. In the current study, C/T and IMI/REL maintained activity against 94 and 91% of P. aeruginosa isolates from patients in ICUs,
with the latter value very similar to the finding in the study by Asempa et al. (90.1% susceptible to IMI/REL) [31].

Among the nonsusceptible subsets, the differences in antimicrobial susceptibility between isolates from ICU and non-ICU wards were smaller and often did not reach statistical significance. For example, susceptibility to ceftazidime was 47.8% and 59.1% among meropenem-nonsusceptible isolates from ICU and non-ICU wards, respectively (p<0.05), while among MDR isolates susceptibility to ceftazidime was 15.7% and 19.3% (p>0.05). C/T and IMI/REL maintained activity against 71% and 66% of MDR \textit{P. aeruginosa} from ICUs, respectively. Even among DTR isolates, a novel category focusing on treatment-limiting resistance to all first-line agents, C/T and IMI/REL maintained activity against 61% and 54% of isolates, respectively. These \textit{in vitro} data are promising, especially for infections with pan-\beta-lactam-nonsusceptible and DTR isolates, although clinical outcome data will be critical in determining the ultimate role of these agents in patient treatment.

CZA, for which data were only available in 2018-2019 in the current study, was active against 51% of DTR ICU isolates, 16 and 5 percentage points lower than observed for C/T and IMI/REL, respectively, using the limited dataset. Only amikacin consistently exceeded the activity of C/T and IMI/REL among nonsusceptible subsets, but is associated with significant morbidity, including nephrotoxicity, and is typically used only in combination with another agent. Furthermore, colistin was until recently considered a last-resort option for treatment of infections caused by resistant isolates; however, the CLSI guidelines consider all \textit{P. aeruginosa} isolates nonsusceptible to colistin, as clinical and PK/PD data demonstrated limited clinical efficacy [28].

The activity of IMI/REL was slightly lower than that of C/T by 3 percentage points, but IMI/REL maintained activity against 58-59% of C/T-nonsusceptible isolates, 28-58 percentage points higher than all comparator agents except amikacin. Similar observations were seen in a recent study of a large collection of \textit{P. aeruginosa} isolates from Spain [20]. Fraile-Ribot \textit{et al.} found susceptibility to IMI/REL among C/T- and ceftazidime/avibactam-resistant isolates that showed resistance mechanisms such as ESBL production (e.g., PER and GES) or AmpC (PDC) mutations [20]. Conversely, C/T maintained activity against 73-78% of IMI/REL-nonsusceptible isolates. Similarly,
when eliminating the more susceptible isolates by limiting the analysis to MDR isolates from ICU patients, a more pronounced proportion of the remaining isolates were susceptible to one of the two agents but not to the other (52 of 140 MDR isolates collected from ICU patients, 37.1%). Given these findings as well as the limited data available for ceftazidime/avibactam in the current study, which also showed cross-susceptibility with C/T and IMI/REL, it appears prudent to include these newer agents in the susceptibility testing protocol, as this increases the chance of identifying an effective agent for infections caused by nonsusceptible \textit{P. aeruginosa} phenotypes that can be very challenging to treat. The combined susceptibility testing of C/T and IMI/REL would identify a potentially effective antibiotic for 98-99\% of all \textit{P. aeruginosa} isolates collected for the current study and may be useful in offering expeditious susceptibility data for clinical use. In fact, given the overarching goal to improve antimicrobial stewardship and timely appropriate therapy, it seems crucial to have susceptibility testing results to all newer agents available as soon as possible, including cefiderocol, which was not included in the SMART testing protocol but has been shown to be a potential treatment option for drug-resistant \textit{P. aeruginosa} [32, 33]. However, given the practical limitations of testing all isolates against these agents, especially the testing of cefiderocol (which requires a special medium), it may be reasonable to restrict testing to isolates collected from patients at risk for resistance or with a history of resistance, or to settings with less than 90\% susceptibility of \textit{P. aeruginosa} to traditional anti-pseudomonal agents. This would be in line with the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) HAP/VAP guidelines which recommend two antipseudomonal antibiotics from different classes for the empiric treatment of suspected VAP in these situations [34]. Early testing of newer agents could decrease considerably the use of combination therapy and result in earlier initiation of adequate therapy against drug-resistant pathogens, potentially leading to better clinical outcomes, shorter hospital stays, and reduced healthcare costs [6, 35-37].
Conclusions

Resistance to C/T or IMI/REL was uncommon among recent LRTI isolates of *P. aeruginosa* collected in the United States. There are differences in the mechanisms that result in resistance to C/T and IMI/REL, as evidenced by a considerable proportion of isolates testing as nonsusceptible to one agent and susceptible to the other, especially among isolates from patients in ICUs. These data suggest that susceptibility testing for both agents should be considered at hospitals, as both IMI/REL and C/T could provide important new options for treating patients with infections caused by nonsusceptible *P. aeruginosa* isolates, especially considering the substantially reduced susceptibilities to commonly used β-lactams.
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Potential Conflict of interest

SHL, KMK, and DFS work for IHMA, which receives funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA for the SMART global surveillance program. DDD, CAD, KY and MRM are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and own stock and options in Merck & Co., Inc., Kenilworth, NJ, USA. The IHMA authors do not have personal financial interests in the sponsor of this paper (Merck Sharp & Dohme Corp.).

Patient Consent Statement

Not applicable; study does not include factors necessitating patient consent.
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Figure 1. Antimicrobial susceptibility to C/T, IMI/REL, and comparators among all collected *P. aeruginosa* isolates from patients in ICUs (n=720) and non-ICU wards (n=914)

*Statistically significant difference between isolates from ICU and non-ICU wards (p<0.05).

C/T, ceftolozane/tazobactam; IMI/REL, imipenem/relebactam; IMI, imipenem; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin/tazobactam; ATM, aztreonam; LVX, levofloxacin; AMK, amikacin
Figure 2. Proportion of isolates with resistant phenotypes among all *P. aeruginosa* collected from patients in ICUs (n=720) and non-ICU wards (n=914)

*Statistically significant difference between isolates from ICU and non-ICU wards (p<0.05).
C/T, ceftolozane/tazobactam; NS, nonsusceptible (intermediate or resistant MICs); IMI/REL, imipenem/relebactam; DTR, difficult-to-treat resistance; MDR, multidrug-resistant; FEP, cefepime; CAZ, ceftazidime; MEM, meropenem; P/T, piperacillin/tazobactam; IMI, imipenem.
Table 1. Antimicrobial susceptibility to C/T, IMI/REL, and comparators among *P. aeruginosa* with nonsusceptible phenotypes

| Phenotype/ward type (n) | Ceftolozane/tazobactam | Imipenem/relebactam | Imipenem | Meropenem | Cefepime | Ceftazidime | Piperacillin/tazobactam | Aztreonam | Levofloxacin | Amikacin |
|-------------------------|-------------------------|----------------------|----------|-----------|----------|------------|-------------------------|----------|--------------|---------|
| **Meropenem-NS**        |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (207)               | 83.1                    | 68.1                 | 4.4      | 0.0       | 45.9     | 47.8<sup>a</sup> | 36.2                    | 26.1     | 27.1         | 90.8    |
| Non-ICU (208)           | 88.9                    | 72.6                 | 9.6      | 0.0       | 48.6     | 59.1<sup>a</sup> | 44.2                    | 31.3     | 29.3         | 92.3    |
| **Piperacillin/tazobactam-NS** |                   |                      |          |           |          |            |                         |          |              |         |
| ICU (228)               | 82.5                    | 77.2                 | 39.9     | 42.1      | 26.8     | 20.2<sup>a</sup> | 0.0                     | 7.9<sup>a</sup> | 34.2         | 91.7    |
| Non-ICU (214)           | 87.4                    | 79.4                 | 47.7     | 45.8      | 34.6     | 31.3<sup>a</sup> | 0.0                     | 15.9<sup>a</sup> | 32.7         | 92.5    |
| **Cefepime-NS**         |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (176)               | 76.7                    | 72.2                 | 34.7     | 36.4      | 0.0      | 11.9<sup>a</sup> | 5.1<sup>a</sup>         | 4.6<sup>a</sup> | 30.7         | 89.2    |
| Non-ICU (179)           | 84.4                    | 77.1                 | 38.6     | 40.2      | 0.0      | 30.2<sup>a</sup> | 21.8<sup>a</sup>        | 18.4<sup>a</sup> | 27.4         | 87.2    |
| **Ceftazidime-NS**      |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (197)               | 78.2                    | 79.2                 | 41.1     | 45.2      | 21.3     | 0.0        | 7.6                     | 9.6      | 38.1         | 90.4    |
| Non-ICU (166)           | 81.3                    | 83.7                 | 45.8     | 48.8      | 24.7     | 0.0        | 11.5                    | 12.1     | 33.1         | 90.4    |
| **Imipenem-NS**         |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (264)               | 87.1<sup>a</sup>        | 75.0                 | 0.0      | 25.0<sup>a</sup> | 56.4     | 56.1<sup>a</sup> | 48.1<sup>a</sup>        | 40.2<sup>a</sup> | 36.0         | 92.1    |
| Non-ICU (282)           | 92.2<sup>a</sup>        | 79.4                 | 0.0      | 33.3<sup>a</sup> | 61.0     | 68.1<sup>a</sup> | 60.3<sup>a</sup>        | 50.4<sup>a</sup> | 40.8         | 92.2    |
| **MDR**                 |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (140)               | 71.4                    | 65.7                 | 15.7     | 18.6      | 11.4     | 15.7       | 5.7                     | 2.9      | 17.9         | 84.3    |
| Non-ICU (114)           | 77.2                    | 67.5                 | 17.5     | 18.4      | 12.3     | 19.3       | 10.5                    | 4.4      | 14.0         | 83.3    |
| **Pan-β-lactam-NS**     |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (90)                | 65.6                    | 56.7                 | 0.0      | 0.0       | 0.0      | 0.0        | 0.0                     | 0.0      | 0.0          | 15.6    |
| Non-ICU (65)            | 72.3                    | 63.1                 | 0.0      | 0.0       | 0.0      | 0.0        | 0.0                     | 0.0      | 10.8         | 84.6    |
| **DTR**                 |                         |                      |          |           |          |            |                         |          |              |         |
| ICU (72)                | 61.1                    | 54.2                 | 0.0      | 0.0       | 0.0      | 0.0        | 0.0                     | 0.0      | 0.0          | 83.3    |
Non-ICU (56) & 69.6 & 57.1 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 82.1 \\
IMI/REL-NS & & & & & & & & & & \\
ICU (66) & 72.7 & 0.0 & 0.0 & 0.0 & 25.8 & 37.9 & 21.2 & 13.6 & 15.2 & 80.3 \\
Non-ICU (59) & 78.0 & 0.0 & 1.7{\textsuperscript{b}} & 3.4 & 30.5 & 54.2 & 25.4 & 17.0 & 11.9 & 81.4 \\
C/T-NS & & & & & & & & & & \\
ICU (43) & 0.0 & 58.1 & 20.9 & 18.6 & 4.7 & 0.0 & 7.0 & 4.7 & 18.6 & 67.4 \\
Non-ICU (32) & 0.0 & 59.4 & 31.3 & 28.1 & 12.5 & 3.1 & 15.6 & 6.3 & 9.4 & 71.9 \\

{\textsuperscript{a}}Statistically significant difference between isolates from ICU and non-ICU wards (p<0.05).

{\textsuperscript{b}}One isolate tested with an IMI/REL MIC of 4 µg/mL (intermediate) and an IMI MIC of 2 µg/mL (susceptible).

NS, nonsusceptible (intermediate or resistant MICs); MDR, multidrug-resistant; DTR, difficult-to-treat resistance.
Table 2. Activity of C/T and IMI/REL against all *P. aeruginosa* collected from patients in (a) ICUs and (b) non-ICU wards

### a) ICU

|                | IMI/REL | Number of isolates |
|----------------|---------|--------------------|
|                | Susceptible | Nonsusceptible    |                  |
| C/T            |           |                    |                  |
| Susceptible   | 629 (87.4%) | 48 (6.7%)          | 677              |
| Nonsusceptible| 25 (3.5%)  | 18 (2.5%)          | 43               |
| Number of isolates | 654     | 66                 | 720              |

### b) Non-ICU

|                | IMI/REL | Number of isolates |
|----------------|---------|--------------------|
|                | Susceptible | Nonsusceptible    |                  |
| C/T            |           |                    |                  |
| Susceptible   | 836 (91.5%) | 46 (5.0%)          | 882              |
| Nonsusceptible| 19 (2.1%)  | 13 (1.4%)          | 32               |
| Number of isolates | 855     | 59                 | 914              |
Table 3. Activity of C/T and IMI/REL against MDR  \textit{P. aeruginosa} collected from patients in (a) ICUs and (b) non-ICU wards

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & \multicolumn{2}{c|}{IMI/REL} & \multicolumn{1}{c|}{Number of isolates} \\
\cline{2-4}
 & Susceptible & Nonsusceptible & \\
\hline
\textbf{C/T} & & & \\
\hline
Susceptible & 70 (50.0\%) & 30 (21.4\%) & 100 \\
\hline
Nonsusceptible & 22 (15.7\%) & 18 (12.9\%) & 40 \\
\hline
Number of isolates & 92 & 48 & 140 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & \multicolumn{2}{c|}{IMI/REL} & \multicolumn{1}{c|}{Number of isolates} \\
\cline{2-4}
 & Susceptible & Nonsusceptible & \\
\hline
\textbf{C/T} & & & \\
\hline
Susceptible & 64 (56.1\%) & 24 (21.1\%) & 88 \\
\hline
Nonsusceptible & 13 (11.4\%) & 13 (11.4\%) & 26 \\
\hline
Number of isolates & 77 & 37 & 114 \\
\hline
\end{tabular}
\end{table}
Figure 1
Figure 2

|        | C/T-NS | IMI/REL-NS | DTR   | Pan-β-lactam-NS | MDR   | FEP-NS | CAZ-NS | MEM-NS | P/T-NS | IMI-NS |
|--------|--------|------------|-------|-----------------|-------|--------|--------|--------|--------|--------|
| ICU    | 6.0    | 9.2        | 10.0  | 12.5            | 19.4  | 24.4   | 27.4   | 28.8   | 31.7   | 36.7   |
| Non-ICU| 3.5    | 6.5        | 6.1   | 7.1             | 12.5  | 19.6   | 18.2   | 22.8   | 23.4   | 30.9   |