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Infect Control Hosp Epidemiol 2017;38:880–881
 0899-823X/2017/3807-0021. DOI: 10.1017/ice.2017.85

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Understanding the β-Lactam/Inhibitor of β-Lactamase Combinations: Reassessment for Better Antimicrobial Stewardship

To the Editor—The β-lactamases are plasmid-encoded or chromosomally encoded enzymes that hydrolyze β-lactam antibiotics. Those that are plasmid-mediated can be rapidly transferred between bacterial genera and can put in check the successful use of β-lactam agents. The β-lactam/inhibitor of β-lactamase (BL/IBL) combinations are a class of agents with proven success in treating infections caused by bacteria producing β-lactamases, mostly the conventional-spectrum enzymes.[1]

The prevalence of gram-negative bacteria resistant to broad-spectrum β-lactams has increased alarmingly in past decades, including those extended-spectrum β-lactamase (ESBL)–producing organisms with poorer clinical outcomes than more susceptible organisms.[2]

Unequivocally, carbapenems have a relatively high clinical success rate among patients infected with ESBL-producing organisms.[3] However, indiscriminate carbapenem use has contributed to the increased emergence of carbapenem-resistant Enterobacteriaceae (CRE).[4]

Because it is crucially important to conserve the usefulness of carbapenems in the era of antimicrobial resistance, a survey was conducted to monitor the contemporary crude prevalence of resistance rates for BL/IBL combinations against *Escherichia coli*, *Klebsiella*, and *Proteus* species displaying a conventional or ESBL-enzyme spectrum, including those presenting a carbapenem-resistance profile but not a carbapenemase production relation.

Enterobacterial isolates were recovered from inpatients between January 1 and December 26, 2016, at a tertiary hospital in Porto Alegre, Southern Brazil. *Escherichia coli*, *Klebsiella*, and *Proteus* species were selected because other minor prevalent enterobacterial species such as *Enterobacter*, *Providencia*, *Serratia*, and *Citrobacter freundii* have an intrinsic resistance to amoxicillin/clavulanate. Biochemical tests using a MicroScan automated system (Beckman Coulter, Brea, CA) were used to identify *E. coli*, *Klebsiella*, and *Proteus* species and to determine their resistance rates to amoxicillin/clavulanate (AMC), ampicillin/sulbactam (SAM), and piperacillin/tazobactam (TZP). All selected enterobacterial isolates were confirmed for the presence of an ESBL enzyme using a synergistic test applying clavulanic acid, as previously described.[2] Isolates with reduced susceptibility to any carbapenem agent were tested using a synergistic test applying phenyl-boronic acid and ethylenediaminetetraacetic acid to detect *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-β-lactamase enzyme, in that order. Only CRE isolates with a negative result for any carbapenemase were included in this study.

A total of 942 isolates were included in this survey; 878 isolates (93.2%) had a community profile: 441 *E. coli* (50.2%); 213 *Proteus mirabilis* (24.3%); 210 *K. pneumoniae* (23.9%); and 14 *K. oxytoca* (1.6%). In addition, 62 isolates (6.6%) had an ESBL-producing spectrum: 53 *K. pneumoniae* (85.5%), 8 *E. coli* (12.9%); and 1 *P. mirabilis* (1.6%). Only 2 isolates (0.2%), *K. pneumoniae*, and *E. coli*, had a carbapenem-resistance profile. Of these isolates, 591 (62.7%) were recovered from urine, 174 (18.5%) were recovered from blood, 92 (9.8%) were recovered from respiratory secretions, 19 (2%) were recovered from catheter tip, and 66 (7%) were recovered from elsewhere.

Resistance rates to AMC, SAM, and TZP for each categorized group (community-based, ESBL-producing, or CRE profile) are shown in Table 1. Overall, among the BL/IBL combinations, TZP was the most active combination (14.6% of resistance rate), followed by AMC (32.3% of resistance rate) and SAM (51.9% of resistance rate). The greatest potency of activity was shown by TZP

TABLE 1. Resistance Rates of BL/IBL Combinations Against *Escherichia coli*, *Klebsiella*, and *Proteus* Species

Enterobacterial Groups (No. of Isolates)	BL/IBL combination (% of resistance in each group)		
	AMC	SAM	TZP
Community spectrum (878)	251 (28.6)	427 (48.6)	108 (12.3)
Extended spectrum (ESBL) (62)	51 (82.2)	60 (96.8)	28 (45.2)
Carbapenem-resistance spectrum (2)	2 (100)	2 (100)	2 (100)
Total (942)	304 (32.3)	489 (51.9)	138 (14.6)

NOTE. BL/IBL, β-lactam/inhibitor of β-lactamase; AMC, amoxicillin/clavulanate; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam; ESBL, extended-spectrum β-lactamase.

in both community-based and ESBL-spectrum profiles. None of the combinations were active in vitro against CRE isolates.

A more liberal use of carbapenems is not without consequence and may result in the emergence of a resistance to this agent[4] as well as others, such as polymyxins[5,6] and fosfomycin,[7] due to the influence of an increased demand, which may severely limit future treatment options.

In this study, tazobactam was the most superior (while sulbactam was the less active) IBL to inhibit β-lactamases, no matter their spectrum, as previously described elsewhere.[1] Notably, these results obtained with TZP may reflect the increased activity of piperacillin. However, the applicable comparison is between amoxicillin and ampicillin due to the overlapping activities of these agents.

Although SAM has historically been favored for its activity against *Acinetobacter*, its activity is no longer observed, and its usefulness is questionable in community-based infections (eg, pyelonephritis, appendicitis, cholecystitis, complicated urinary infections, and others), which often require hospitalization and more appropriate empirical therapy protocols. For community-acquired infection of mild-to-moderate severity in adults, SAM is not recommended because of high rates of resistance to this agent among community-acquired *E. coli*, according to the guidelines by the Surgical Infection Society and the Infectious Diseases Society of America.[8] Therefore, would nosocomial use of AMC (endovenous) not be more appropriate than SAM?

Regardless, some important factors may influence this option: First, although the addition of IBLs appears to reduce the hydrolyzing effect of β-lactamase enzymes on the β-lactam ring, their activity is diminished when a high concentration of bacteria is present, cf, "inoculum effect."[9] These contrasting distributions may be important because respiratory tract infections imply in a high inoculum of bacteria in a compartment where penetration of antibiotics may be impaired, whereas urinary tract infections have a more moderate inoculum and β-lactams easily concentrate in the urine. Second, the presence of other mechanisms of β-lactam resistance, such as *amp*C β-lactamase overproduction or additional ESBLs, certainly act by reducing the activity of BL/IBLs.[10] Third, our results are disturbing because the use of any BL/IBL combination is already ineffective against >10% of resistant organisms and should not be used unless hospital surveys indicate >90% susceptibility, as indicated for quinolones, for example.[8]

In conclusion, our results show the superior activity of TZP among the BL/IBL agents regardless of the profiles presented by the isolates. The use of SAM must be questioned (and even replaceable by AMC) due to the high resistance rates observed. Further studies are required to confirm our findings in other nosocomial populations.

ACKNOWLEDGMENTS

Financial support: No financial support was provided relevant to this article.

Potential conflicts of interest: The author reports no conflicts of interest relevant to this article.

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Infect Control Hosp Epidemiol 2017;38:881–883

 0899-823X/2017/3807-0022. DOI: 10.1017/ice.2017.93

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Transmission of ST8-USA300 Latin American Variant Methicillin-Resistant *Staphylococcus aureus* on a Neonatal Intensive Care Unit: Recurrent Skin and Soft- Tissue Infections as a Marker for Epidemic Community-Associated-MRSA Colonization

To the Editor—We report a mother-to-newborn transmission of ST8-USA300 Latin American Variant methicillin-resistant *Staphylococcus aureus* (MRSA) on a neonatal intensive care unit during kangaroo mother care in a German University Hospital, which raises the question of whether recurrent skin and soft-tissue infection (SSTI) is an important marker for colonization with epidemic MRSA clones. The clonal expansion of the particularly virulent MRSA strain pulsotype USA300 is much dreaded. USA300 is the predominant MRSA clone circulating in the community in the United States, and it is recognized as a common cause of nosocomial *S. aureus* bloodstream infections, increasingly blurring the classic distinction between community- and hospital-associated MRSA.[1] A variant of this virulent strain, designated as the Latin American Variant of USA300 MRSA (USA300-LV), was able to infiltrate, disseminate, and become the predominant MRSA in the community as well as in healthcare settings across most of Latin America.[2]

Although international travel and migration fosters the global spread of *S. aureus*,[3,4] detection of USA300-LV in Europe is rare[1,3] and generally occurs in subjects with close family or travel links to Latin America.[3] Nevertheless, the first observations of its autochthonous spread in the community have been reported in Spain and Italy.[1] To date, in-hospital transmission of USA300-LV is an entirely unknown phenomenon in Europe, in contrast to Latin America, where it accounts for a substantial proportion of the nosocomial MRSA infections in Columbia and Uruguay.[1,2]

In October 2016, preoperative screening revealed Panton-Valentine leucocidin–positive (PVL+) MRSA isolated from a nasal swab of a 16-day-old, premature newborn (gestational age 33 weeks 2 days; 1,360 g) that had been hospitalized since birth due to a congenital heart anomaly (index case) (Table 1). Two days later, MRSA was also detected in the nose and breast milk of the mother, who at that time provided kangaroo mother care (ie, skin-to-skin care) to her child on a daily basis.[5] Because a postpartum screening of the child had been negative for multidrug-resistant organisms and because no other patients with MRSA colonization or infection had been treated on the same unit at that time, transmission from the mother is the most likely source of USA300-LV in the newborn. This finding is in line with research from Japan that found kangaroo mother care on the neonatal intensive care unit (NICU), although perceived to protect against infectious disease outcomes by increasing the diversity of the baby's microbiome,[5] to be associated with 3.82-fold increased odds of MRSA infection (95% confidence interval, 1.11–13.13).[6]

Searching for the source of MRSA, a medical history among family members revealed recurrent SSTIs in the father and the 4-year-old sister of the index case patient. Swabs of the father's nose and from a resolving purulent SSTI on the sister's leg screened positive for PVL + MRSA. Although decolonization measures were immediately initiated, the mother's cesarean section wound became infected and PVL + MRSA USA300-LV could be cultured from the wound and stitch on day 24 after birth.

All family members received immediate MRSA eradication treatment according to the institutional protocol. The child was isolated for the rest of the hospital stay. Active screening did not detect transmissions to other patients on the same ward. No further cases of MRSA infection have occurred on the NICU unit since October 2016.

All strains isolated were of the *spa* type t008 (ST8), PVL positive, arginine catabolic mobile element (ACME) negative and bear the *SCCmec* type IVc, which is consistent with the ST8-USA300-LV MRSA clone. None of the family members reported significant travel outside Europe in the last 24 months, in particular, not to the United States or Latin America. However, the father of the index case had returned from a trip to Spain more than 12 months previously and prior to suffering from recurrent SSTI.

Among other risk factors, current guidelines recommend screening of intercontinental travelers and patients with active skin infections, prior hospitalization, or contact to patients carrying multidrug-resistant organisms (MDRO) for carriage of MDRO upon admission.[7,8] In the presented case, the mother of the index patient did not fulfill any of the locally implemented criteria and was thus not screened on admission for C-section. Hence, to increase the sensitivity of CA-MRSA detection in the future, we propose targeted screening of all patients reporting recurrent SSTI defined as 2 or more episodes within the last 12 months in either (1) themselves or (2) members of the same household. This rationale is supported by reports on (1) recurrent skin infection being linked

https://doi.org/10.1017/ice.2017.93 Published online by Cambridge University Press