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Activity of imipenem/relebactam against Gram-negative bacilli from global ICU and non-ICU wards: SMART 2015–2016

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ABSTRACT

Objectives: Antimicrobial resistance is increasing worldwide and is especially problematic in ICUs. Relebactam is a new bicyclic diazabicyclooctane β-lactamase inhibitor of class A and C β-lactamases that is in development in combination with imipenem. This study describes geographical resistance patterns among isolates from ICU and non-ICU wards in seven global regions and examines the activity of imipenem/relebactam in these settings.

Methods: In 2015–2016, 194 hospitals from 55 countries each collected up to 100 consecutive Gram-negative pathogens from intra-abdominal, 100 from lower respiratory and 50 from urinary tract infections per year. Susceptibility was determined for 45 699 non-Proteeae Enterobacteriaceae (NPE) and 10 834 *Pseudomonas aeruginosa* using CLSI broth microdilution and breakpoints, with imipenem breakpoints applied to imipenem/relebactam.

Results: Isolates from ICUs were more resistant to almost all tested agents across regions and infection sources. The size of the ICU/non-ICU difference varied, with a smaller gap in USA/Canada and South Pacific (regions with highest susceptibility) and for imipenem/relebactam, amikacin and colistin (drugs with highest activity). Susceptibility of NPE to imipenem/relebactam was >90% in ICUs in all regions except Africa (88.2%). Only amikacin exceeded these rates in most regions. Against cefepime-non-susceptible and multidrug-resistant (MDR) NPE from ICUs, imipenem/relebactam maintained activity >90% in three regions and >80% in the remaining regions except Africa (75%). Susceptibility of *P. aeruginosa* was >90% in ICUs in USA/Canada, South Pacific and Europe and >82% elsewhere.

Conclusions: Imipenem/relebactam could provide a valuable therapeutic option in ICUs, especially against MDR isolates and those non-susceptible to other β-lactam antibiotics.

1. Introduction

Antimicrobial resistance among Gram-negative bacterial isolates is increasing worldwide and is especially problematic in intensive care units (ICUs), a setting where studies have reported especially high resistance levels [1–5], where the risk of acquiring resistant isolates is increased [5–7] and where the patients are especially vulnerable. Moreover, multidrug resistance is a rising problem in ICUs and can severely limit therapeutic options [1,8,9]. Infection with a multidrug-resistant (MDR) isolate greatly increases the risk that antibiotic(s) used will be ineffective, resulting in increased mortality, length of hospital stay and costs in patients with serious infections [10]. Therefore, clinicians tend to prescribe broad-spectrum antibiotics to ICU patients, which in turn may drive increasing antimicrobial resistance rates, including to last-resort agents such as carbapenems [11,12]. These factors illustrate the need for antimicrobial surveillance, especially in ICUs. Continuous monitoring of resistance patterns provides clinicians with critical information to help choose antibiotics for empirical therapy and at the same time supplies data that can help encourage and monitor antimicrobial stewardship efforts. This is especially important since many surveillance programmes have shown that resistance patterns vary greatly geographically [13–16], including the degree to which susceptibility levels differ between ICU and non-ICU wards. For example, in one study the susceptibility of Enterobacteriaceae both in ICU and non-ICU wards was lower in Europe than in North America, and the gap between susceptibility levels in ICUs and non-ICU wards was substantially larger in Europe [4].

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The global Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored the antimicrobial susceptibility of Gram-negative bacilli from intra-abdominal infections (IAIs) since 2002 and from urinary tract infections (UTIs) since 2009. In 2015, lower respiratory tract infections (RTIs) were added to the collected specimen sources, and imipenem/relebactam was added to list of tested agents. Relebactam, formerly MK-7655, is a new non-β-lactam bicyclic diazabicyclooctane β-lactamase inhibitor that is structurally related to avibactam (the non-β-lactam β-lactamase inhibitor recently approved for use in combination with ceftazidime). Relebactam is in clinical development in combination with imipenem/cilastatin and restores the in vitro activity of imipenem against Enterobacteriaceae and *Pseudomonas aeruginosa* that carry class A or class C β-lactamases. Its activity spectrum includes *Klebsiella pneumoniae* carbapenemase (KPC)-producers as well as *P. aeruginosa* isolates that are carbapenem-resistant due to impermeability arising from porin loss combined with elevated production of AmpC, a common carbapenem resistance mechanism in *P. aeruginosa* [17,18]. Imipenem/relebactam has shown promising activity against non-Proteeae Enterobacteriaceae (NPE) and *P. aeruginosa* in several in vitro studies [17,19–21], has successfully completed phase 2 clinical trials and is currently in phase 3 development for the treatment of complicated IAIs, complicated UTIs and bacterial pneumonia, including hospital-acquired pneumonia and ventilator-associated pneumonia [22].

The current study had two objectives: (i) to describe geographical resistance patterns for commonly used antimicrobial agents among recent isolates from ICU and non-ICU wards in seven global regions; and (ii) to add to the limited in vitro data available for imipenem/relebactam by examining its activity against Gram-negative bacilli from ICUs compared with non-ICU wards, including the activity against isolates non-susceptible to β-lactams and MDR isolates.

2. Materials and methods

2.1. Clinical isolates

For the SMART programme, participating sites each collected up to 250 consecutive aerobic or facultatively anaerobic Gram-negative bacterial isolates per year (up to 100 from IAIs, up to 100 from RTIs and up to 50 from UTIs). Only one isolate per species per patient was accepted. Following species identification using local site procedures, all isolates except those from China and India were sent to one of two central laboratories [International Health Management Associates, Inc. (IHMA), Schaumburg, IL or IHMA Europe Sàrl, Monthey, Switzerland] where their identities were confirmed using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonics, Billerica, MA). In 2015 and 2016, 194 hospital laboratories from 55 countries in Africa (5 countries), Asia (11 countries), Europe (17 countries), Latin America (11 countries), Middle East (6 countries), South Pacific (3 countries) and the USA/Canada collected 66 865 isolates of Gram-negative bacilli from ICU and non-ICU wards. Supplementary Table S1 shows the countries that participated in each region as well as the number of submitted isolates. Enterobacteriaceae accounted for 49 705 isolates (74.3% of all Gram-negative organisms) and *P. aeruginosa* accounted for 10 834 isolates (16.2%). The current study excluded 6326 isolates of non-Enterobacteriaceae Gram-negative bacilli other than *P. aeruginosa* largely because of known intrinsic resistance to imipenem (e.g. *Stenotrophomonas maltophilia* and *Burkholderia* spp.) and known limited activity of imipenem and imipenem/relebactam (e.g. *Acinetobacter* spp.) [19,21,23]. Also excluded were Proteeae Enterobacteriaceae ($n = 4006$; 6.0% of all Gram-negative organisms) as this tribe is intrinsically resistant to imipenem by a mechanism other than production of carbapenemases [24]. Relebactam, as an inhibitor of class A and class C β-lactamases, is not expected to increase substantially the susceptibility of Proteeae to imipenem, and imipenem/relebactam is not expected to be an antimicrobial agent of choice against these species. Among the 45 699 NPE, 11 884 isolates were from patients in ICUs [of which 4118 (34.7%) were from IAIs, 6205 (52.2%) were from RTIs, 1478 (12.4%) were from UTIs and 83 (0.7%) were from an unspecified source] and 33 815 isolates were from patients in non-ICU wards [of which 17 386 (51.4%) were from IAIs, 6314 (18.7%) were from RTIs, 9884 (29.2%) were from UTIs and 231 (0.7%) were from an unspecified source]. Among the 10 834 *P. aeruginosa* isolates, 3812 isolates were from patients in ICUs [of which 574 (15.1%) were from IAIs, 3015 (79.1%) were from RTIs, 203 (5.3%) were from UTIs and 20 (0.5%) were from an unspecified source] and 7022 isolates were from patients in non-ICU wards [of which 2013 (28.7%) were from

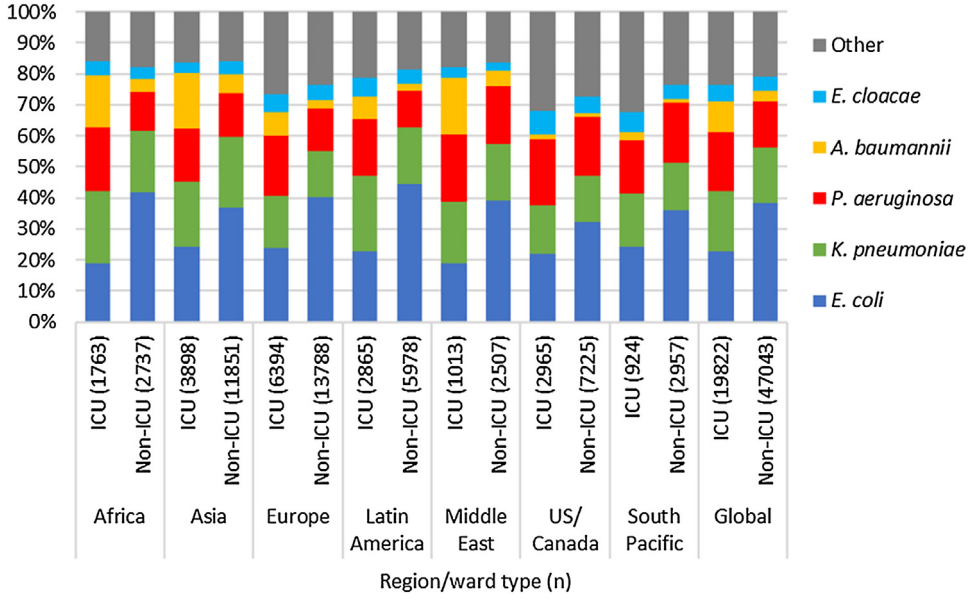

Fig. 1. Species distribution among all Gram-negative bacilli by region and ward type, 2015–2016. ICU, intensive care unit.