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Highlights in ASM MICROBE 2017 (New Orleans)

Marina Peñuelas[1]
Clara Lejarraga[1]
Carla Rico[1]
Berta Laguna[1]
Avelina Suárez[1]
Francisco Javier Candel[1,2]

[1]Department of Clinical Microbiology. Hospital Clinico San Carlos. Madrid. Spain.
[2]Health Research Insitute (IdISSC). Hospital Clinico San Carlos. Madrid. Spain.

The following manuscript intends to give an overview of the main topics presented during the ASM Microbe 2017 held from June 1 to 6 in New Orleans (LA, US), with special focus on those more novel and/or controversial topics; taking into account the impossibility of summarizing the totality of the communications.

For a better comprehension, the manuscript is divided into four sections: Gram-positive infections, Gram-negative infections, new antimicrobial agents and new antifungal agents.

GRAM-POSITIVE INFECTION

Infections caused by multidrug-resistant Gram-positive bacteria represent a major number of infections in our hospitals. Consequently, new drugs are being investigated and tested, and a large number of studies have been carried out.

The SENTRY surveillance program, as a part of a larger study, measured the activity of fusidic acid against 1,000 strains of methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible coagulase-negative *Staphylococcus* (MS-CoNS), and methicillin-resistant coagulase-negative *Staphylococcus* (MR-CoNS). Samples were collected from different hospitals in the USA. The results showed that only 1.7% of strains were resistant to this antibiotic (Sat-56).

Another project compared linezolid 600 mg/12h versus fusidic acid (FA) 1500 mg/12h during the first two days, followed by 600 mg/12h. Both were oral treatments during 10 days over skin and soft tissue infections. The results showed no-inferiority of FA due to an early clinical response after the first dose during the first 48-72h. FA also achieved microbiological success in 100% of patients who finished the treatment, and there was no difference relative to secondary effects (AAID LB21).

Another large study was conducted in USA under the AWARE surveillance program in the ICU ward with elderly hospitalized patients with pneumonia. The activity of ceftaroline and ceftriaxone was measured in 2.250 pneumonia etiologic pathogens. Ceftaroline was active over all the bacterial pneumonia etiologic agents in the ICU, even against *Streptocccus. pneumoniae* penicillin-resistant. In addition, MICs were lower than with other antibiotics tested (Sun-5, Harris K.; Sun-24).

In the CAPTURE study experience, 188 patients with community acquired bacterial pneumonia (80.9%) and hospital acquired/ ventilator associated pneumonia (19.1%) were treated with ceftaroline fosamil. The results obtained showed a high clinical success rate when using doses of 600mg/12h, and a very low mortality index (Fri-35. Undeani G.).

On the other hand, persistent infection has been subject of clinical concern lately. Oritavancin, dalbavancin and vancomycin were tested against non-dividing MRSA. The bacterial viability was assessed by serial dilution planting, and results were measured by fluorescence microscopy. Oritavancin achieved higher logarithm reduction than vancomycin and dalbavancin (Belley A. et al).

Dalbavacin bactericidal effect, when daily dosing was applied for endocarditis therapy caused by *S. aureus* with elevated MIC, was evaluated in a Pk/Pd murine model. The aim of this study was to investigate if the results could be extrapolated to humans. Different doses were trialed, showing that using high loading doses (300-700 mg) followed by a maintenance dose (30-70 mg), allowed the target attainment to be achieved (Farkas A. Mount Sinai).

In another remarkable study at ASM Microbe 2017, oritavancin was tested against 1.500 strains of Gram-positive bacteria commonly isolated in blood-stream infections (BSI), and bone and joint infections (BJI). Just 2% of the strains were

Correspondence:
Francisco Javier Candel González
Department of Clinical Microbiology. Health Research Institute (IdISSC). Hospital Clínico San Carlos. UCM. Madrid.
Avda Profesor Martín Lagos S/N. 28040. Madrid.
E-mail: fj.candel@gmail.com

resistant to this antibiotic. Overall, oritavancin demonstrated larger *in vitro* potency than comparison agents did. Regarding BJI, oritavancin also demonstrated high *in vitro* activity, including MRSA (Mendes RE. Sun-33; Fri-342).The results suggest that this antibiotic is promising but requires more clinical experience.

Moving on to vancomycin-resistant *Enterococcus* (VRE), it is worth remembering an article published in 2015 with the results of treating bloodstream infections with daptomycin. Authors wrote about the seesaw effect of daptomycin when using in combination with β-lactams antibiotics, in cases in which daptomycin MIC was over 2 mg/L (Moise PA. Clin Ther 2016). Another study was presented, reflecting 177 BSI by VRE and treated with daptomycin at doses of 8-10 mg/kg. Patients were divided in two groups depending on the MIC of daptomycin: MIC ≤ 2 mg/L (n=33) and MIC = 3-4 mg/L (n=144). There was no difference in clinical success, focus control or adverse effects (Fri-217).

By finishing this Gram-positive review, it is worth noting the international study carried out in which tedizolid was tested against 612 strains of Gram-positive cocci obtained from bone infection. All 100% of the strains were susceptible, and showed a MIC < 0.5 mg/L. According to that, tedizolid would be an attractive alternative for treating BJI (Fri-217).

GRAM-NEGATIVE INFECTION

Plazomicin activity, when MIC is tested under non-standard conditions, is comparable to that of amikacin, with a negligible effect of increasing or decreasing the bacterial inoculum, the addition of human serum or lysed horse blood, variations of Mg^{2+} o Ca^{2} concentration and growth in 5% CO_2 atmosphere or at pH of 8. In addition, two known characteristics of the aminoglycosides were confirmed, such as the reduction of their activity under conditions of acid pH or anaerobiosis (Fri-410).

On a Brazilian study (Martins A.) focused on testing the susceptibility to aminoglycosides, with 500 carbapenemase-producing Enterobacteriaceae (CPE) strains, mainly KPC-2 (n=399) and NDM-1 (n=79), plazomicin obtained a lower MIC than the cut-off point in 90% of isolates, with a MIC mode and median below 0.5 mg/L. In the comparative study, gentamicin showed more than 90% of resistance, and amikacin showed an MIC_{50} of 8 mg/L (4 dilutions higher than that obtained with plazomicin).

Another study compared the efficacy and safety of plazomicin treatment for severe infections (BSI, NAP and VAP) produced by CPE. Colistin was used as comparator. Doses used in this study were 15 mg/kg/24h of plazomicin as 30 minutes infusion and 5 mg/kg/8-12h of colistin with a loading dose of 300 mg. Both antibiotics were used in combination with others such as meropenem or tigecycline, with a total treatment length between 7 and 14 days. Plazomicin got reductions in all-causes mortality at day 28, bacteremia related mortality at day 28, toxicity and a greatest microbiological response.

Getting into communications related to β-lactam antibiotics, we start with a study (Fri 53) which tested aztreonam/avibactam (AZT/AVI) activity against 267 strains of class B CPE (120 NDM-like, 82 VIM-like, 27 IMP-like, 22 NDM+OXA-48 like, 8 VIM+OXA-48 like, 6 VIM+KPC and 2 IMP+KPC) obtained from different geographical localizations all over the world. All strains were susceptible to AZT/AVI with an improved activity than aztreonam.

A study from the Mayo Clinic (Karau M.) compared the *in vitro* activity of piperacillin/tazobactam (PIP/TZ), ceftazidime, cefepime, meropenem (MER) and ceftazidime/avibactam (CAZ/AVI) against *Pseudomonas aeruginosa* isolates from patients admitted to ICU ward. CAZ/AVI turned out to be the β-lactam with the highest susceptibility percentage (89.9%), showing a MIC ≤ 4 mg/L in 78.3% of the strains and a MIC ≤ 8 mg/L in 89.9% of total cases. MER obtained 76.8% susceptibility, with 84.1% and 88.4% of the strains showing a MIC ≤ 4 mg/L and MIC ≤ 8 mg/L respectively.

Regarding the activity of CAZ/AVI against *P. aeruginosa* strains obtained from the INFORM global surveillance program of 2015 data was presented (Fri-51). In total, 90.8% of the strains (n = 3.462) were susceptible to CAZ/AVI, increasing to 94.7% when only non-metallo-carbapenemases producer strains were considered (n = 3.319). In addition, among multidrug-resistant strains (MDR) that do not produce metallo-carbapenemases, 30.7% (n = 540) were non-susceptible, showing that there are mechanisms of resistance other than metallo-carbapenemases.

The therapeutic success of CAZ/AVI was also evaluated in a retrospective cohort study among patients at the University of Pittsburg Medical Center (Fri 8) who received 3 or more days of definitive treatment for carbapenems-resistant (CR) *Klebsiella pneumoniae* bacteremia. In this study, the outcomes of those patients treated with CAZ/AVI were compared with those achieved with the rest of the therapeutic options. Clinical success and survival rates were improved among patients treated with CAZ/AVI compared to alternative regimens for CR *K. pneumoniae* bacteriemia. At the same time, CAZ/AVI was associated with lower rates of acute kidney injury than regimens containing colistin or aminoglycosides.

On the other hand, a Canadian study (Fri 48) evaluated the activity of several β-lactams against Gram-negative bacilli obtained from the CANWARD study. According to this study, CAZ/AVI was found to be more active than ceftolozane-tazobactam (CT/TZ) in all cases except *P. aeruginosa*. Another study (Fri 50) showed potent activity of C/T against various resistant phenotypes including extended spectrum β-lactamase (ESBL), colistin non-susceptible, MDR and extreme-drug-resistant isolates.

It was very remarkable a Spanish communication (Sun LB-15), that showed, for the first time, the existence of a resistant strain to these new combinations of cephalosporin-betalactamases inhibitor (CAZ/AVI and CT/TZ) due to the duplication of an aminoacid at the active site of an OXA-2 betalactamase (class D) of the high-risk clone ST235.

Regarding the new combination of meropenem with vaborbactam (MER/VAR), it was reported a study (Fri 58) that showed an improvement of the carbapenemic activity against classes A and C betalactamases, achieving a decrease in MIC of 4 to 6 folds lower than MER. This combination has been approved by the FDA for urinary infections treatment, including pyelonephritis, after demonstrating greater efficacy, safety and tolerance than PIP/TZ. Regarding the preliminary results of the TANGO-1 study (Kaye KS.) on urinary bacteremia, MER/VAR was successful in 83%-100% of the cases at the end of the intravenous treatment (IV), while PIP/TZ obtained 60%-75%. In the case of BLEE carrier isolates, success at the end of IV treatment was 94%-98% and 56%-66% for MER/VAR and PIP/TZ respectively. Patients with a higher Charlson were worse, without differences between both groups (Shorr A.). Regarding the average stay, something similar happened; this was greater in the more comorbid ones, without differences between the assigned treatments (Shorr A.).

Finally, there were many and remarkable communications about cefiderocol, a new cephalosporin drug, characterized by a strong chelating ability to Fe^{3+} as well as siderophores. Cefiderocol penetrates bacteria using iron transporters, present in multiple Gram-negative bacteria, such as enterobacteria and non-fermenting bacilli. A study was presented in which the activity of cefiderocol was evaluated against more than 1,000 Gram-negative bacilli not susceptible to MER, with more than half carrying carbapenemase, mainly OXA-23 (n=543). Cefiderocol showed high activity, with MIC_{50} and MIC_{90} several dilutions below the cut-off point (≤4 mg/L) (Sun 25). It was notably, however, that only 58.3% of NDM-1 producing enterobacteria and 85.7% of GES producing *Acinetobacter baumannii* were susceptible, although the resistant strains showed CMI one fold above the cut-off. In addition, cefiderocol proved to be more active than colistin, CT/TZ, CAZ/AVI and ciprofloxacin (Sun 11).

NEW ANTIMICROBIAL AGENTS

During the last years, there has been special interest in the development of new therapeutic options against ESKAPE pathogens (VRE, MRSA, ESBL and CR *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* sp.).

The optimization of novel monobactams for stability against serine β-lactamases has led to the identification of LYS228. The mechanism of action of LYS228, which is similar to that in aztreonam, consist on binding to PBP3 lowering its affinity to the PBP1AB. LYS228 is highly efficient in the presence of all classes of β-lactamases, and it is not affected by metallo-β-lactamases. It also has good stability against ESBLs, including the cephalosporinases, and also shows high activity against carbapenemases (CTX-M, KPC, OXA) Enterobacteriaceae isolates. It has been found mutations in regulators cell wall stress and efflux pumps. It has a preclinical pharmacokinetic profile, pharmacokinetic/ pharmacodynamic profile similar to aztreonam. Phase I studies are ongoing (Sat-297).

The New Agents Discovery Summary Session presents ACT051, a novel aryloxazolidinone- linked bacterial topoisomerase inhibitor (NBTIs), with heavy activity against ESKAPE pathogens. Typical NBTIs, have activity against VRE, MRSA and *A. baumannii*. ACT051 has potent activity against all ESKAPE pathogens, and retained activity against resistant strains to major antibiotic classes. (Sat-261, 262, 263, 264, 265. Sun-210).

Finally, the ARB- Antibiotics Hybrids, presented by the Kings College of London. They introduce a work hypothesis, talking about de association between two molecules, one of them (low molecular weight proteins) which disrupt the efflux pumps function, leading to elevated intracellular concentration of the second molecule (e.g. fluoroquinolone). These studies are still in the design phase.

NEW ANTIFUNGAL AGENTS

Invasive fungal disease represents a growing medical problem due to several factors, with special emphasis on the increasing implementation of treatments that suppress the immune system, with the consequent failure or inability to fight off opportunistic fungi. Currently available treatments for deep-tissue fungal infections have low survival rates, and are associated with a range of serious complications along with side-effects. Drug resistance is also a very significant issue, with high impact on treatment availability for critical patients. The following is a short description of 3 novel therapeutic options to this significant clinical problem, presented at the ASM Microbe 2017.

NP339 (Novamycin®) is a broad spectrum antimicrobial, active against clinically challenging pathogenic yeast and filamentous fungi. Its mechanism of action consists on charge-charge dependent interaction between NP339 (cationic) and fungal cell membrane (anionic) leading to membrane perturbation and lysis. This mode of action rapidly neutralizes both non-metabolizing and metabolically active fungi. It is important to highlight that NP339 also prevents biofilm formation. Novamycin® represents a potential antifungal peptide that rapidly kills target pathogens in such a way as to minimize the chances of drug resistance, especially on yeast and probably not that much on some filamentous fungi.

VL-2397 represents a potentially new class of antifungal agents. Invasive aspergillosis is the starting point of the development roadmap. This antifungal agent presents a novel mechanism of action; it occurs via Sit1 (a non-existent transporter in mammalian cells), so its activity results from effect on an intracellular target (Denning D, Science 2015). Phase 1 clinical trial showed that VL-2397 appears to be safe and well tolerated with favorable plasma PK profiles in healthy subjects.

The investigational product is currently in a Phase 2 trial. The multicenter, open label randomized clinical study, will compare the efficacy and safety of VL-2397 to standard treatment for invasive aspergillosis in acute leukemia patients and recipients of allogeneic hematopoietic cell transplant. The pri-

mary endpoint of the trial is all-cause mortality at 4 weeks and the key secondary endpoint is all-cause mortality at 6 weeks. The trial will be conducted at selected sites in North America, Europe and Asia. (Sean M. Sullivan, June 03 2017).

On the other hand, VT-1161 is a potent and selective, orally administered inhibitor of fungal CYP51, which has successfully completed Phase 2b clinical trials for the treatment of recurrent vulvovaginal candidiasis (RVVC) and onychomycosis. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane. It has demonstrated unprecedented efficacy in RVVC patients, with as low as 0% recurrence rates through 48 weeks. This treatment option seems to be safe and well tolerated, with an adverse event profile similar to placebo. These results suggest that VT-1161 may be a promising agent to treat RVVC, a condition associated with a very high burden of disease and for which there are no approved therapies; besides VT-1161 may avoid the side effects that limit the use of current oral antifungal therapies, such as liver toxicity and drug-drug interactions. (Sun-AAID LB21).