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**Non-Interventional Study (NIS) Report Synopsis**

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**CERBERUS: Multicenter study of antimicrobial resistance of Gram-positive and Gram-negative clinical strains to ceftaroline and other antimicrobials in Russia**

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**Study dates:**

**First Subject In:** October 12, 2012

**Last Subject Last Visit:** December 30, 2012

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## REPORT SYNOPSIS

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### **CERBERUS: Multicenter study of antimicrobial resistance of Gram-positive and Gram-negative clinical strains to ceftaroline and other antimicrobials in Russia**

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#### STUDY SITES

Isolates collected from 36 Russian cities were included in the study and analyzed in two central microbiological laboratories.

#### STUDY DATES

**First strain in:** Q3 2012

**Last strain in:** Q4 2012

#### OBJECTIVES OF THIS NON-INTERVENTIONAL / IN VITRO MICROBIOLOGICAL STUDY

Primary objective:

To estimate antimicrobial activity of ceftaroline and other commonly used antimicrobials addressing clinically relevant strains of *Staphylococcus aureus* (MRSA and MSSA), *Streptococcus pneumoniae* (including multi-resistant strains), *Streptococcus pyogenes*, other representatives of *Streptococcus* (including *S. milleri* group), *Haemophilus influenzae* and non-producing ESBL Enterobacteriaceae from various regions of Russia using CLSI breakpoints.

Secondary objectives:

- To estimate how susceptibility of various microorganisms to ceftaroline and other antibiotics is influenced by infection localization, medical condition, ward/unit profile, patient profile (age, gender).
- To estimate change of antimicrobial activity of ceftaroline and other antibiotics on strains collected from 2008 to 2012.

#### STUDY DESIGN

Isolates were collected retro- and prospectively in multicentre microbiological *in vitro* study.

## TARGET SUBJECT/ISOLATE POPULATION

3,009 of clinically relevant isolates of above described species from respective sources (e.g. wounds, sputum, sinus aspirate, blood etc.) were collected from 36 Russian cities from 2008 to 2012.

## STUDY VARIABLES

Primary variable:

Percentage/numerical MIC distribution of microorganisms for ceftaroline and other tested antimicrobials, including MIC<sub>50</sub> and MIC<sub>90</sub>, percent/quantity of susceptible and resistant strains in accordance with CLSI recommended breakpoints.

Secondary variables:

- Percentage/numerical MIC distribution of microorganisms, including MIC<sub>50</sub> and MIC<sub>90</sub>, percent/quantity of susceptible and resistant strains, to tested antimicrobials depending on infection localization, medical condition, ward/unit profile, patient profile (age, gender).
- Percentage/numerical MIC distribution of microorganisms, including MIC<sub>50</sub> and MIC<sub>90</sub>, percent/quantity of susceptible and resistant strains, to ceftaroline and other antimicrobials from 2008 to 2012.

## STATISTICAL METHODS

Descriptive statistics was used in the study. MIC distribution will be calculated using geometric mean.

## STUDY RESULTS

A total of 3,009 consecutive non-duplicate isolates were collected during multicentre microbiological in vitro study from 36 geographically distinct cities of Russia during 2008-2012 years. Most isolates included in the study were considered to be clinically relevant by microbiologist or physician. Among tested strains 1000 were *Staphylococcus aureus* (including 612 – MRSA), 954 – *Streptococcus pneumoniae*, 338 – beta-hemolytic streptococci, 401 – Enterobacteriaceae (all-ESBL-negative), 85 – *Haemophilus influenzae* and 231 – *Acinetobacter* spp.

Species identification of collected isolates was initially performed at the local hospital laboratories. Identities of all isolates were subsequently confirmed using Microflex LT MALDI Biotyper System (Bruker Daltonics, Germany) at the central microbiological laboratories: microbiological laboratory of the Institute of Antimicrobial Chemotherapy of the Smolensk State Medical Academy Smolensk Russia and microbiological laboratory of the Scientific Research Institute of Pediatric Infections of Federal Medico-Biological Agency Saint-Petersburg Russia.

**Primary outcome:**

Overall susceptibility rates to ceftaroline were 89.7% for *S. aureus* (100% for MSSA, 83.2% for MRSA), 99.5% for *S. pneumoniae*, 100% for beta-hemolytic streptococci, 98.8% – for *H. influenzae* and 75.8% for non-ESBL producing Enterobacteriaceae.

### **Secondary outcomes:**

The detailed data are presented in Tables 4-57 of the study report.

#### *S. aureus:*

MRSA rate was 61.2% which was higher than lastly reported in multicentre studies (49.9%), indicating continuous spread of resistant clones on territory of Russian Federation. Susceptibility rate to vancomycin was 99.5% for MRSA, though 69.6% had MIC=1 mg/L and 18.3% - MIC=2 mg/L, that might be a subject of potential concern from clinical point of view. Of a particular interest, 60.4% of strains resistant to ciprofloxacin, that might reflect inadequate overuse in out-patient settings.

#### *S. pneumoniae:*

Penicillin non-susceptibility (3.7%) is generally a somewhat previously reported in Russia, though erythromycin non-susceptibility (15.5%) exceed those typically found in previous nationwide studies. Interestingly, clindamycin is active against 6.5% of erythromycin non-susceptible isolates suggesting circulation of *mef*-producing *S. pneumoniae* in Russia.

#### Beta-hemolytic streptococci:

Expectedly, no penicillin resistant isolates have been found. Of a particular concern, extremely high (53.0%) non-susceptibility to tetracycline.

#### *H. influenzae:*

There were 11.8% of ampicillin-resistant strains found, which substantially exceeds those previously reported. Potential BLNAR were detected in 2.3% of cases. There was no azithromycin resistance found.

#### Enterobacteriaceae:

Co-trimoxazole and ciprofloxacin resistances were found in 26.7% and 26.2% of isolates, respectively, potentially reflecting inadequate use of these antimicrobials. Of a particular concern, presence of 0.7% and 1.7% resistant strains to meropenem and ertapenem, respectively, indicating the emergence of problem of carbapenem-resistant Enterobacteriaceae.

#### *Acinetobacter* spp.:

In general, *Acinetobacter* spp. resistances were higher than expected. 88.7% of resistance to ciprofloxacin minimizes its potential use for the therapy of infections caused by this pathogen. More than 2/3 of acinetobacters (67.1%) were resistant to imipenem, indicating prevalence of carbapenem-resistant isolates in circulating strains population.

No geographical or year-to-year differences were found in susceptibility to any tested antimicrobials independently on the location of participating centers, either stratified by the hospital and/or federal region.

Ceftaroline exhibited potent activity *in vitro* against a variety of major Gram-positive and Gram-negative pathogens, including MRSA, in this large selection of geographically and temporally diverse 2008-2012 isolates in Russia. No geographical and year-to-year differences were found in susceptibility to any tested antimicrobials independently on the location of participating centers, either stratified by the hospital and/or federal region. Higher than previously reported incidence of MRSA potentially indicates continuation of spread of resistant MRSA clones in Russian Federation. Of the greatest concerns are emergence of carbapenem-non-susceptible Enterobacteriaceae and also predominance of carbapenem-resistant *Acinetobacter* spp.