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NOSOCOMIAL PATHOGENS AND ANTIBIOTIC RESISTANCE

Nosocomial infections caused by antibiotic resistant bacteria are challenging for healthcare professionals and for our entire society. Clinicians and pa-tients in intensive care units (ICU)s experience the greatest burden from nosocomial infections mostly because of the broad use of invasive devices, and therefore new approaches in treatment as well as in diagnostics are urgently needed for ICU infections. This article discusses some advances in the diagnostics and treatment of healthcare-associated infections in ICU. One is related to diagnostics of nosocomial meningitis. We found the presence of bacteria, in select cases of post-neurosurgical aseptic meningitis. Another ongoing research project reveals the benefits of transferrin in the treatment of nosocomial pathogens Acinetobacter baumannii and Klebsiella pneumoniae in vitro.

Ershova K.

Introduction. Antibiotic resistance crisis

On August 11, 2010 two newspaper articles were published simultaneously on the opposite sides of the world. Both of them-one in the American *New York Times titled* «Antibiotic-Resistant Bacteria Moving From South Asia to U.S.» [1] and a second one «NDM-1 superbug patient at St Mark's Hospital in *Harrow treated* with special infection controls» [2] published in Britain's Harrow Times-discussed the emergence of extremely drug-resistant bacteria in their respective countries. Healthcare experts and the scientific community had commented that

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described pathogen, "[suggested] a serious problem" [1]. Both articles were referring to a *Klebsiella pneumonia* strain carrying the carbapenem resistance gene *bla*NDM-1, which was first described in 2009 in a patient who had been travelling in India [3]. The ability of this bacteria to survive in the presence of all known antibiotics caused a significant concern among healthcare professionals and the public. *bla*NDM-1 gene had been spreading over the world very fast, exploding into a public health emergency. By 2010 the *bla*NDM-1 gene was found in the U.S. and U.K. [4], and by the next year in Japan [5], and then virtually all across the globe. It is just one of the most recent examples of the public taking note of this growing threat coming from resistant bacteria. Other prominent examples took place about 10-20 years ago and included the public uproar over MRSA, like in this article with a frightening headline «Super-resistant superbug» in the CBS News in 2004 [6].

Historically, the problem of antibiotic resistance has evolved side by side with the use of antibiotics, and began with Alexander Fleming and the discovery of penicillin. A. Flemming was the first person, who acknowledged the problem of antibiotic resistance emerging under the selective pressure of antibiotics, and in his Nobel Lecture strongly suggested physicians and the public should not misuse antibiotics: «…Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant» [7]. However, over the last 80 years mankind ended up in the antibiotic resistance crisis [8]. This strong definition, together with words like «superbugs», «postantibiotic era», and «the killer germ» began to ap-pear in the press more and more frequently in the last couple decades, aiming to alarm society about the catastrophe with antibiotic resistance. The level of mass media involvement highlights that the crisis goes far beyond the only healthcare system problem, but affects the well-being of the entire population.

While the public is becoming more aware of the antibiotic resistance crisis, for physicians it has already been a constant issue. The problem of nosocomial infections is especially relevant for critical care medicine. Intensive care specialists are usually the first who deal with the new resistant bacterial strains, therefore it is particularly important for them to stay up-to-date on this topic and adopt the very best clinical practices.

According to CDC report from 2002, about 25% of all nosocomial infections in the U.S. occurred among adults and children in ICUs [15]. Other studies demonstrated similar results [17]. Many aggressive interventions, such as mechanical lung ventilation, urinary, venous and arterial catheters, etc., must be done to save lives of ICU patients. These invasive devices disrupt the integrity of the body surface and become the main risk factor increasing hospital-acquired-infection morbidity in ICU. The National Nosocomial Infection Surveillance (NNIS) system reported in 2000 that 83% of episodes of nosocomial pneumonia were associated with mechanical ventilation; 97% of urinary tract infections occurred in patients with a urinary catheter; and 87% of primary bloodstream infections were in patients with a central line [16]. Hospital-acquired infections in ICUs affect mortality rate significantly. In some patient groups, e.g. elderly patients treated with central catheter and/ or mechanical ventilation devices in ICUs, in-hospital mortality was 4 times higher than in those without nosocomial infections

[17]. Because of the nature of the ICUs, critical care specialists cannot completely eliminate health care associated infections and must pay great attention to this issue worldwide.

This article describes research projects, conducted by critical care specialists and anesthesiologists in collaboration with basic science research labs and clinical institutes in 2016-2017. The projects are united by the topic of hospital infections and regard the problems of diagnostics and treatment of such infections.

Diagnostics is a challenge

Diagnostics of nosocomial infections can be challenging due to multiple factors including the anatomical site of infection and the pathogen species. Fortunately, new technologies are able to improve diagnostics significantly. The use of diagnostic PCR helped to support suspicions about bacterial involvement in some cases of aseptic postoperative meningitis [9]. Prior to that more than half of all cases were considered to be aseptic [10, 12]. Thereby achievements in molecular-biology techniques revealed that the prevalence of hospital infection is higher than it was thought. Nowadays modern methods such as high-throughput sequencing are able to detect the microorganisms which cause infection process, but cannot be detected by routine methods.

Post-neurosurgical meningitis has been a controversial topic in terms of diagnostics and treatment for a long time. It significantly impairs prognosis for patients, enhances mortality rate and prolongs hospitalization [11]. A number of reasons complicate diagnostics of postoperative infection meningitis, such as mild and unspecific clinical representation against the background of the immediate postoperative period, unclear interpretation of CSF lab results, and often negative cultural test (golden diagnostic standard for bacterial meningitis). In such circumstances, critical care physicians face uncertainty when determining the appropriate treatment. That promotes the misuse of antibiotics and influences patient's outcome negatively.

Aseptic post-neurosurgery meningitis was a subject of our research. A 2007 study estimates the level of negative results of cultural methods to be 60-75% of all cases of postoperative meningitis [12]. However, it was first shown in the study from 1996 that not all of those cases are truly aseptic [9]. PCR with universal bacterial primers revealed the presence of bacterial DNA in the CSF samples, which were considered to be aseptic based on cultural analysis. That particular study included 3 groups: 7 patients with post-neurosurgical meningitis and culture-positive, 20 patients with post-neurosurgical meningitis and culture-negative, and 30 patients without meningitis as negative control. PCR with 16S rRNA primers was done and result was positive for all patients with culture-positive CSF, negative for all in the negative control group and positive for 13 out of 20 patients with culture-negative CSF [9]. Authors concluded by saying «Many cases of culture-negative (aseptic) meningitis are probably bacterial meningitis and justify antibiotic treatment» [9]. This result became a paradigm shift for neurosurgeons as well as for critical care specialists, and further research were required. Most recent meta-analysis in this topic (from 2012) showed that PCR with 16S rRNA primers were positive in 30% of cases of culture-negative postoperative meningitis [13]. Based on the 14 studies included in the meta-analysis, the authors suggested 16S PCR as a diagnostic tool in bacterial meningitis and a useful supplement to the cultural methods [13].

In collaboration with Burdenko Neurosurgical Institute (Moscow, Russia) a pilot study was started in 2016. The project goal was to search for bacterial DNA in the CSF in cases of culture-negative postoperative meningitis in neurosurgical patients followed by identification of bacterial species based on 16S sequencing.

Material and methods

3 patients with clinical signs of post-neurosurgery meningitis, but with culture-negative CSF and negative results of qRT-PCR with standard diagnostic panel were enrolled in the study[1]. CSF samples were taken from the patients; DNA was purified from the samples. PCR was performed with universal 16S rRNA bacterial primers 27F&1492R. PCR products were purified and cloned into E.coli in order to compose16S rRNA library. For proof-of-principle, a few random colonies were selected for further study. Plasmids with 16S fragment were purified from those colonies and sequenced using Sanger method. Sequences were identified in NCBI and SILVA databases using BLAST algorithm [14]. Twenty one clones from the library were studied in total.

Results

Bacterial DNA was found in CSF from all patients in the study. Propionibacterium, Enterobacter and other Gram-negatives, as well as Staphylococcus spp. were the most frequent findings. In addition, there were a number of unique and unexpected findings, such as Psychrobacter, Corynebacterium, and Microbacter, which occurred in individual cases. All of those bacteria been previously reported as a cause of meningitis. The entire list of bacterial species found in CSF of three patients is presented in Table 1. Thus, we found bacterial DNA in 100% of studied cases of culture-negative («aseptic») postoperative meningitis. Interestingly, a mixed bacterial population was identified in each CSF sample, but we revealed just a part of that biodiversity in the samples due to method limitations.

Discussion

There are a number of modern technologies, which are helpful to study the etiology of nosocomial meningitis in much more precise and sophisticated way. Next generation sequencing (NGS) and metagenomic sequencing technologies just recently were adopted in postoperative meningitis research. Such technologies appear to be breakthroughs. Dr. Charles Chiu from University of California, San Francisco in 2014 said: «Metagenomic sequencing identifies a pathogen that other technologies missed» [18]. The first study identifying the bacterial pathogen Leptospira santarosai by NGS in case of culture-negative meningitis was published in 2014 [19]. A year later, studies reported Balamuthia mandrillaris [20] and Psychrobacter spp. [21] found in CSF from patients with meningoencephalitis. In 2016 the research paper about the use of solid brain tissue NGS to study neuroinfections in 10 patients revealed many advantages of NGS technology [22]. In the cases of our patients, metagenomic sequencing would be particularly helpful to clarify the entire biodiversity in the samples. Nevertheless, based on our research and previous data there is a

Table 1 - **Bacterial species found in CSF of three patient**

Patient #1		
Bacterial species	Identity, %	Length, bp
Propionibacterium;	100	812
Enterobacter;	99.5604	934
Propionibacterium;	99.6849	956
Corynebacterium 1;	98.6547	970
Escherichia-Shigella;	99.4792	966
Staphylococcus;	99.0816	990
Propionibacterium;	99.4437	844

Patient #2		
Bacterial species	Identity, %	Length, bp
Propionibacterium;	99.8879	892
Propionibacterium;	99.4426	953
Enterobacter;	99.4675	939
Pseudomonas;	99.0674	965
Neisseriaceae;	91.4136	970
Propionibacterium;	99.1027	1004
Propionibacterium;	99.3111	871

Patient #3		
Bacterial species	Identity, %	Length, bp
Psychrobacter;	98, 913	997
Microbacterium;	99.2693	962
Staphylococcaceae; Jeotgalicoccus;	99.2144	966
Microbacterium;	98.9806	980
Escherichia-Shigella;	99.6939	988
Microbacterium;	99.0731	971
Sphingomonas;	99.1878	1018

reason to believe that in some cases of post-neurosurgical aseptic meningitis bacteria are involved. However, the etiological role of bacteria found in our study is unclear. Further research is needed to clarify the causality of found pathogens in meningitis.

Treatment is a challenge

The American Centers for Disease Control and Prevention (CDC) in 2013 has assigned the highest level of threat to three bacterial species: Clostridium difficile, carbapenem-resistant Enterobacteriaceae (CRE) and drug-resistant Neisseria gonorrhoeae [23]. For CRE it means that those bacteria have become resistant to all or almost all available antibiotics. In February of 2017 the World Health Organisation (WHO)

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[1]diagnostic panel of specific primers for Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Staphylococcus spp, Enterobacteriaceae, Streptococcus spp, Enterococcus spp, Candida spp (Candida albicans, C.glabrata, C.krusei, C.parapsilosis и C.tropicalis), Toxoplasma gondii, Listeria monocytogenes

published its first list of antibiotic-resistant «priority pathogens» ever, in order to recognize the big threat of resistant bacteria as well as to encourage pharmaceutical companies to do R&D in antibiotics [24]. Priority #1 in this list are again the Gram-negative pathogens — Acinetobacter baumannii (carbapenem-resistant), Pseudomonas aeruginosa (carbapenem-resistant), Enterobacteriaceae (carbapenem-resistant and ESBL-producing). The increasing role of these bacteria in morbidity and mortality and their dramatically rapid spreading in the world urgently implore us to address this issue and search for new treatment options.

A CDC survey reported that in 2014 in the U.S. the percent of CRE ranged from 0–27.9% (3.5% nationally), the percent of Acinetobacter resistant to at least 3 different antibiotics (multidrug-resistant Acinetobacter) ranged from 5.0% to 88.1% (54.8% nationally) [25]. In Russia the majority of isolated clinical strains of A. baumannii are multi-drug resistant: 93% of them are resistant to cefoperazone, 61,2% to amicacin, 51,9% to levofloxacin [26]. The crisis of antibiotic resistance among Acinetobacter and CRE species together with the misuse of existing antibiotics support the idea that antimicrobials with novel mechanisms of action are needed.

We are currently actively investigating if transferrin will be an effective adjunctive antimicrobial against antibiotic-resistant Gram-negative bacteria— Klebsiella pneumonia and Acinetobacter baumannii. This ongoing research is focused on decreasing the emergence of resistant mutants by using a novel combination of antibiotics with recombinant human transferrin (rh-transferrin). We hypothesize that rh-transferrin would exert less selective pressure as compared to traditional antibiotics. It has been reported in previous studies that transferrin which cause iron starvation in bacteria but does not interact with any molecular targets on bacterial surface, has broad antimicrobial effects in vitro against Gram-positive and Gram-negative bacteria and fungal pathogens [30].

Transferrin functions by passively starving the bacteria of iron needed for microbial replication [31]. 10-6 M concentration of intracellular iron is required for bacterial survival, however in mammals, the concentration of free ionic iron is maintained at <10-24 M, primarily by transferrin [27]. It is believed that such a low concentration of iron was an ancient mechanism of antimicrobial defence in mammals. It is a promising idea to decrease the concentration of free iron in a host organism to induce the iron starvation in bacteria to prevent their growth. One drug was developed based on this idea but unfortunately it failed in controlled clinical trials because of poor safety and lack of efficiency [28]. As it was found, the chelating agent (small molecule) caused iron deficiency in the host organism together with iron accumulation in the kidney which led to adverse events. The use of transferrin is appealing because utilizes a normal iron sequestering pathway and is therefore less likely to cause problem with iron metabolism, and thus may overcome limitations of small chelating molecules. Furthermore, rh-transferrin has already been studied in clinical trials and no observable toxicity was found [29]. Iron is a universal requirement for all human path-ogens, thus the potential applications of iron-blocking therapy can be very broad. This novel therapeutic strategy will be able to optimize current treatment for life-threatening Gram-negative infections and improve the clinical outcomes.

The main goal of this project is to study the in vitro and in vivo effect of adjunctive transferrin on susceptibility and emergence of resistance in the Gram-negative pathogens Acinetobacter baumannii and Klebsiella pneumoniae. The research is currently ongoing, however we already received clear evidences that rh-transferrin containing therapeutic regimens suppressed the emergence of resistance in vitro, and is promising as an adjunct to antibiotic therapy. Future plans include animal experiments in mouse bacteremia model to ensure efficacy in vivo.

Conclusion

The environment of ICUs, patient population and treatment involving plenty of invasive devices contribute to the high rate of nosocomial infections in ICU. As a direct consequence, generally ICUs utilize the most antibiotics in the hospital. For instance, in Switzerland the median of total antibiotic use in hospitals was 53.4 defined daily doses (DDD) per 100 bed-days, whereas the median in ICUs was 114.3 defined daily doses (DDD) per 100 bed-days [33]. It is consistent with the European data [34]. The presence of resistant bacteria in ICUs enhances antibiotic consumption noticeably. Taking another example from Europe, in 2011 the growth in the number of cases of resistant K. pneumonia in ICUs resulted in three times increase of carbapenems usage [32]. Considering that selective pressure from antibiotics provokes the formation of antibiotic resistance, the vicious circle is closing. It makes critical care doctors feel frustrated and literally fight for each patient, and make governments establish the policies to combat antibiotic-resistant bugs [35, 36]. However, as Dr. Spellberg highlighted in his lectures: «We have to stop viewing our relationship with microbes as a war because there is no endgame. Instead, the goal is the policy that seek sustainability over centuries.». One of the hypotheses how to decrease re-sistance is tested in ongoing research project. By this moment we demonstrate that transferrin could be a promising agent for combination antimicrobial therapy of Acinetobacter baumannii and Klebsiella pneumoniae. Another research which was done showed that new diagnostic technologies can significantly improve differential diagnostics in cases of post-neurosurgical meningitis and therefore make the use of antibiotic more intelligent and precise.

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PARADIGM SHIFT IN THINKING OF PERIOPERATIVE ANALGESIA

This is a reflection of our quarter century experience at the University of Southern California in Los Angeles which has three multi-disciplinary medical centers with public and private hospitals under one roof. We provide anesthesiology service to approx. 32000 patients per year. LA County USC is the largest trauma center in the western United States. There are approximately 200 ICU beds in all specialties. The Keck School of Medicine is amongst the oldest in the country established in 1885.

Historically we as anesthesiologists have focused our attention on the intraoperative period and to some extent at the immediate postoperative period regarding the patient's experience and analgesia needed for the proposed surgery. Poorly managed pain can lead to complications and prolonged rehabilitation. We use some syringes to anesthetize patient, maintain their hemodynamics, respiratory and vital organ functions by controlling a dial on gas vaporizer or through intravenous fluids and intravenous medications. Towards the end of surgery we use another few syringes to terminate the anesthetic, wakeup our patients and provide postoperative opioid analgesia.

The scope of anesthesiology is now being extended into a larger perioperative role. This begins from the time surgeons decides to operate on a patient until the patient has recovered. This means the focus is now on prehabilitation before surgery which tends to strengthen muscles, manage anxiety and avoid starvation before the catabolic process of surgery. The focus is also on change in analgesic modality of preoperative, intraoperative and postoperative prescription with multi analgesic receptor concept. This also includes use of regional anesthesia and extended duration of regional analgesia with continuous catheters when possible. This approach prevents the acute perioperative pain transitioning to chronic pain. The preponderance of evidence shows that postoperative pain predicts chronic pain. For example, after cardiac surgery, patients with high levels of postoperative pain are 3.5 times more likely to suffer from chronic pain compared to patients with lower postoperative pain levels[6]. The ultimate advantage is improving quality, safety and efficacy with improved outcome perioperatively.

The British journal of anesthesia published a meta-analysis that compared the effectiveness of intramuscular opioids, PCA, epidural analgesia and combined techniques using the aforementioned modalities[5]. The authors found that after IM opioids alone, 67% of patients had moderate and 30% had severe pain. After PCA, 36% had moderate and 10% had severe pain. After epidural analgesia with local anesthetic and opioids, 28% had moderate and 8% had severe pain. When using mixed techniques 30% of patients had moderate and 11% had severe pain. While the epidural analgesia produced the best results,

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