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ANTIBIOTIC THERAPY IN PROBLEMS OF NOSOCOMIAL INFECTIONS

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Nosocomial infections belong to the main reasons decreasing possibilities of effective treatment of many diseases all over the world. They generate huge costs for the healthcare system, and appear in all hospitals — the better hospital, the higher number and seriousness of infections. Regarding different resistance mechanisms of bacteria, synthesis of new antibiotics in pharmaceutical concerns is not sufficient.

Invasiveness of an intensive care refers mostly to the necessity of artificial respiratory route, enabling respiratory therapy, bladder catheterization, and central venous cannulation. These procedures, facing decreased capacity of an immune system, diabetes, and obesity of many patients, contribute to infections' development.

There are no hospitals avoiding nosocomial infections successfully. They rather aims at infections' percentage less than 5–7% of patients. This is the most obvious problem at intensive care units (ICU). This phenomena is well shown in the EPIC (European Prevalence of Infection in Intensive Care) survey. 1417 intensive care units have been evaluated during one day, with more than 10 thousands of patients; 45% of patients were infected, including 47% with pneumonia.

Key words: antibiotic therapy, nosocomial infections, intensive care units.

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ПРОБЛЕМА АНТИБИОТИКОТЕРАПИИ ПРИ НОЗОКОМИАЛЬНЫХ ИНФЕКЦИЯХ

Внутрибольничные инфекции относятся к основным причинам уменьшения эффективности лечения многих заболеваний во всем мире. Они являются причиной огромных расходов на систему здравоохранения и обнаруживаются во всех больницах, чем лучше больница, тем серьезнее и многочисленнее инфекции. Синтез новых антибиотиков является недостаточным для решения проблемы фармакорезистентности бактерий.

Инвазивность в отделении интенсивной терапии связывают с частым применением таких методов, как искусственная вентиляция легких, катетеризация мочевого пузыря, использование центральных венозных катетеров. Эти процедуры, вместе со снижением способности иммунной системы, диабетом и ожирением у многих пациентов, способствуют развитию инфекции. Таким образом, проблема нозокомиальных инфекций является одной из самых актуальных проблем в современной медицине.

Ключевые слова: антибиотикотерапия, нозокомиальные инфекции, отделение интенсивной терапии.

Nosocomial infections belong to the main reasons decreasing possibilities of effective treatment of many diseases all over the world. They generate huge costs for the healthcare system, and appear in all hospitals — the better hospital, the higher number and seriousness of infections [6].

Invasiveness of an intensive care refers mostly to the necessity of artificial respiratory route, enabling respiratory therapy, bladder catheterization, and central venous cannulation. These procedures, facing decreased capacity of an immune system, diabetes, and obesity of many patients, contribute to infections' development [4].

There are no hospitals avoiding nosocomial infections successfully. They rather aim at infections' percentage less than 5–7% of patients. This is the most obvious problem at intensive care units (ICU). This phenomena is well shown in the EPIC (European Prevalence of Infection in Intensive Care) survey. 1417 ICUs have been evaluated during one day, with more than 10 thousands of patients. 45% of patients were infected, including 47% with pneumonia [5].

Regarding different resistance mechanisms of bacteria, synthesis of new antibiotics in pharmaceutical concerns is not sufficient. 16 antibiotics were synthesized in the years 1983–1987, while only the two of them — in the years 2008–2009 [1].

It seems that infection prophylaxis, new legal rules, modern sterilization, funds for disinfection and cleaning, and in particular personnel awareness concerning hygienic principles in everyday patients' care, can be the most effective weapon. As prosaic activity as hand washing before and after contacting a patient, and alcohol disinfection, significantly decreases number of infection and costs of treatment. It was confirmed in many research, analyzing correlation between effectiveness of prophylaxis and prevention programs, volume of antiseptics' usage, frequency of bacteriological testing, and number of infections. Many units have decreased the number of infections by 30–50%, observing the above rules.

Among antiseptics, the first place belongs to 0.5% chlorhexidine added to spirit, and as a water solution 0.12–0.2% used in everyday mouth hygiene of intubated patients, preventing pneumonia this way [7].

Particularly dangerous bacteria, namely alarm pathogens (MDR — multi-drug resistant), have numerous resistance mechanisms. Individual strains have developed the following mechanisms:

1. *Staphylococcus aureus* — methicilin-resistant (MRSA), vancomycin-intermediate (VISA), and vancomycin-resistant (VRSA).
2. *Enterococcus spp.* — vancomycin-resistant (VRE).
3. *Enterobacteriaceae* with ESBL resistance mechanism; KPC+ mechanism; β-lactamases AmpC type.
4. *Streptococcus pneumonia* — penicillin-resistant.
5. *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Stanotrophomonas maltophilia* — multiresistant nonfermenting bacilli produce zinc-containing β-lactamase enzymes (MBL).
6. *Clostridium difficile* — the strain of 027 ribosome, particularly difficult for treatment and eradication.
7. *Candida glaborata*, *Candida krusei* fungi, fluconazole-resistant.
8. A few bacteria developed natural antibiotic resistance, of which particularly important for practice are: cephalosporin-resistant *Enterococcus*, carbapenem-resistant *Stenotrophomonas maltophilia*, colistin-resistant *Proteus spp*., aztrenoam-resistant *Acinetobacter spp*., and *Mycoplasma pneumonia* resistant on β-lactamase antibiotics.

Antibiotic therapy regarding pathogens' resistance is presented in the Table 1.

Colistin is the only alternative in therapy of multi-resistant Gram-negative bacteria. This antibiotic has not been used for many years, due to the possible therapy with less toxic antibiotics of better tissue penetration. Aerosol metanosulfonic colistin is recommended in pneumonia treatment as an adjuvant therapy in 40,000 u/kg bm dose every 8 hours or in monotherapy in 200,000 u/kg bm every 8 hours [2; 3].

Two new antibiotics were registered in Europe in 2012: cephtaroline (Zinforo®) from the 5th group of cephalosporins, with spectrum against *Staphylococcus* MRSA and *Enterobacteriaceae* ESBL additionally. It is registered for skin and skin structure infections and community-acquired pneumonia (activated by MRSA).

The other one is fidaxomicin (Dificlir®), against *Clostridium difficile* infections. It is more effective than vancomycin, regarding in particular frequency of infection recurrence [4].

The following antibiotics have also been introduced recently:

1. Linezolid (Zyvoxid®) — used against MRSA *Staphylococcus*, VRE *Enterococcus*, or *Streptococcus pneumoniae*.

2. Tigecycline (Tygacil®) — of a most broad-spectrum among all the antibiotics, including *Staphylococcus* (MRSA included), VRE *Enterococcus*, Gram-negative bacteria with ESBL mechanism, multi-resistant *Acinetobacter baumanii*, and *Anaerobic bacteria*. However, its producer does not support its usage against pneumonia, and FDA (Food and Drug Administration) recommends tigecycline only in case of total resistance to any other antibiotic.

There are also new fluoroquinolones, like levofloxacin (Tavanic®), which advantage (vs. cyprofloxacin) is better effect in *Streptococcus pheumoniae* treatment. It is a medicine of choice in *Legionella pneumophila* infections treatment. Another one is moxifloxacin (Avelox®), which — apart from levofloxacin advantages — has also better effects in Gram-positive coccuses and anaerobic bacteria, but in the latter infections it shall be associated with another antibiotic, ex. metronidazole.

Fundamental rules of antibiotic therapy

1. Antibiotic shall be administered as soon as possible, after sampling material for bacteriological culture. According to the Surviving Sepsis Campaign, the medicine shall be administered within an hour since infection is confirmed. It is of particular importance in case of meningitis.

2. Antibiotic(s) therapy shall be continued until the resistance result is available, to assure the broadest possible spectrum of activity.

3. Maximal doses of antibiotics shall be administered.

4. Therapies' duration is different. Shorter (up to 8 days) treatment, if the primary therapy was effective, is recommended in pneumonia. Infections within abdominal cavity, after surgical intervention, shall not exceed 47 days (clindamycin shall not be applied empirically regarding high-resistance of *Bacteroides fragilis*).

5. Blood infections (mostly catheter-related) require longer treatment, usually 10–14 days.

6. Fungal infections require the longest treatment: 14 days since a septic culture.

7. Mono-therapy vs. combined therapy: mono-therapy is sufficient in case of bacteria susceptible to antibiotics of good tissue penetration in most infections (excluding *Pseudomonas spp*.).

However, increasing resistance and necessity of using different qualities of antibiotics encourage in some cases to therapy based on two or even three antibiotics. General rule refers to their synergy effect, ex. β-lactamase antibiotics joined with aminoglycosides or fluoroquinolones. Alternative possibilities of joining antibiotics are shown in the Table 2.

8. Method of antibiotic administration can influence its concentration in blood, depending on their pharmaco-kinetic characteristics. Effects of the β-lactamase antibiotic group depend on whether minimal inhibitory concentration (MIC) is being kept between doses. This can be easy reached by administering antibiotic in 3 hrs infusion or permanent, 24 hrs infusion, always after administering first, introducing dose (bolus). We are most experienced in administering meropenem this way, but piperacillin

Table 1

Clinical Implications of Acquired Resistance

Type of resistance	Bacteria	Clinical implications
ESBL	*Klebsiella pneumoniae* and *oxytoca*, *E. coli*, other Gram-negative less often	In major infections — carbapenems of choice; increasing resistance against penicillin with inhibitors — to be used only in urinary tract's infections, with concentration control (E-test), possible resistance against fluoroquinolones, tygecycline, aminoglycosides, cotrimoxazole; total resistance against all cephalosporines
β-lactamases AmpC	*Enterobacter spp.*, *Serratia marcescens*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*	Carbapenems of choice; resistance against cephalosporines of 1–3 generations; penicillin with inhibitor only in *B. fragilis* treatment; questionable effect of cephalosporine of 4th generation
Carbapenemases	*Pseudomonas spp.*, *Acinetobacter spp.*	No treatment options aside from colistin. Tygecycline, sulbactam — *Acinetobacter spp.* only
MBL	*Enterobacteriaceae*, *Stenotrophomonas maltophilia*	Ticarcillin/sulbactam, cotrimoxasole, fluoroquinolones, tygecycline
KPC	*K. pneumoniae, E. coli*, other *Enterobacteriaceae* and *Pseudomonas spp.* less often	Resistance against all β-lactamase antibiotics, including these combined with β-lactamases' inhibitor. *In vitro* sensitivity to colistine, tygecycline, less often gentamicin and amikacin (no clinical data confirming their effectiveness in therapy)
Loss of outer protein	*Pseudomonas spp.*	No treatment options aside from colistin
MBC increase against MIC	*Streptococcus viridans*	20–30% penicillin-resistant, cephalosporines of 1–2 generation of choice, cefotaxime, ceftriaxone
Staphylococcus penicillinase	*Staphylococcus* MSSA	Resistance against penicillin, ampicillin/amoxicillin, ticarcillin, piperacillin. Cloxacillin of choice, then penicillins with inhibitors, cephalosporins of 1–2 generation, ceftriaxone, cefotaxime, cefepime

Resistance against meticiliin	*Staphylococci — aureus*, epidermidis, haemolyticus meticillin-resistant	Resistance against all β-lakctamase antibiotics except cefalosporines of 5th generation. Available treatment: vancomycin, dalfopristin, linezolid, teicoplanin (np MRCNS), quinupristin/dalfopristin, tygecycline, ceftaroline. MRCN-combined therapy: vancomycin + rifampicin + aminoglycosides (against sensitive strains)
Medium sensitivity and resistance against vancomycin	*Staphylococcus aureus* VISA, VRSA	Ceftobiprole? Ceftaroline? Linezolid. Resistance against all β-lactamase antibiotics and vancomycin. Medium sensitivity to *in vitro* vancomycin shall be taken as a clinical resistance
Enterococcus VRE resistance	*Enterococcus faecium*	Resistance against vancomycin and VanA teicoplanin — potential therapy: linezolid, quinupristin/dalfopristin, tygecycline. Resistance against VanB Vancomycin — teicoplanin, linezolid, quinupristin/dalfopristin, tygecycline. VanC resistance — sensitivity to all the antibiotics listed above
Erythromycin-resistance due to impossible antibiotics administration or removal	*Streptococcuses, Staphylococcuses*	Resistance against clarithromycin and azithromycin
Mosaic genes	*Streptococcus pneumoniae*	Penicillin of choice, if sensitivity is confirmed. Actually, treatment starts from cephalosporines of 3rd generations (ceftriaxone, cefotaxime) or levofloxacin. In pneumonia (and sensitivity confirmed) macrolde can be combined. In meningitis — cephalosporine of 3rd generation can be combined with rifampicin, decreasing production of brain toxin pneumolysin, or with vancomycin — if sensitivity to cephalosporines of that generation is not confirmed
Penicillin-resistance	*Neisseria meningitidis*	Penicillin of choice (approx. 6% resistance in Poland). Other possibilities — ceftriaxone, cefotaxime
	Streptococcus pneumoniae	Penicillin of choice (14–80% resistance, depending on geographical region, 30% in Poland). Other possibilities — ceftriaxone, cefotaxime, ceftaroline
High MBC for penicillin	*Streptococcus viridans*	Minimal germicidal concentration for penicilline can be 10 times higher than MIC. Other possibilities — cephalosporines of 1–2 generations, ceftriaxone, cefotaxime

Table 2

Alternative Antibiotics' Combinations

Antibiotic	Combination
Clindamycin	Cephalosporines, aminoglycosides, aztreonam
Macrolides	Metronidazole, cephalosporines, colistin, rifampicin, fluoroquinolon
Tygecycline	Aminoglycosides, piperacillin/tazobactam, imipenem, colistin, aminoglycosides, piperacillin/tazobactam, imipenem, cotrimoxasole
Piperacyllin/ tasobactam	Imipenem, rifampicin, colistin, cotrimoxasole
β-lactamases	Aminoglycosides, fluoroquinolones, β-lacamases (ampicillin + cefotaxime, piperacyllin or cepharosporines, aztrenoam, ertapenem + doripenem)
Colistin	Rifampicin, azithromycin, carbapenems, β-lactamases inhibitors with ampicillin, ticarcillin or piperacyllin, ceftazidime, ciprofloxacin, cotrimoxasole

with tazobactam and ceftazidime were also infused this way. Administering single, large dose of β-lactamase antibiotic can exceed MIC value 4 or 5 times, but with no improvements in therapy.

9. The effect of aminoglycosides depend on the proportion between concentration in infection site against MIC. It shall reach 8–10, i.e. the antibiotic shall be administered in a large, single dose. It is valid also for the whole group of fluoroquinolones, to be used in maximal doses in serious infections.

Fungal infections are more lethal than bacterial ones, inter alia because of late diagnosis. In *Candida spp*. infections (abdominal and catheter-related infections), with sepsis symptoms (hypotension), echinocandins are recommended.

10. The risk of teratogen effect of antibiotics shall not be forgotten.

Relatively safe antibiotics include inhibitor-free penicillin, cephalosporin, aztreonam, and meropenem. Aminoglycosides, linezolid, imipenem, and nitrofurantoin can alternatively be used, however they pose some kind of threat. Sulfonamides, antifungal imidazole medicine, or metronidazoles shall not be administered.

Viruses, *TB mycobacteria*, and anthrax terrorist attacks make global epidemiological threat. The SARS (severe acute respiratory syndrome) epidemic in 2003 was kind of virus threat, when no treatment was effective, and only symptomatic measures were employed. Almost 8000 people fell sick in 23 countries in short time, 643 of them died.

Biological weapon is a potential threat as well. Easy to produce, cheap (in ratio to human losses on 1 square kilometer it amounts to 1 USD, while 800 USD for nuclear weapon, and 1500 USD for conventional weapon), invisible in attack, with infection symptoms difficult for diagnosis, extremely effective. Atomization of 50 kg of anthrax bacteria over 0.5 mln city results in 15 thousand of death, and 125 thousand of infected people.

It is estimated, that 1/3 of global human population is TB infected. WHO forecasts that approx. 1 bln people will be TB infected in 2020, and 150 mln will die of TB. This problem refers in 95% to poor, underdeveloped countries.

HIV infections shall not be marginalized as well.

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