C. Lanckohr

Rational use of antibiotics in the era of multi-resistance

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Summary

The growing rate of resistance development is making the treatment of many types of infections more difficult while the application of reserve antibiotics is increasing. Unfortunately, the new development of antibiotics has stagnated at a very low level for years, and especially substances with a novel mechanism of action are hardly available. This problem is noticeable particularly in the field of Gram-negative bacteria. One relevant mechanism of antibiotic resistance is the expression of β-lactamases, which in several different ways causes resistance to β-lactam-antibiotics. Combinations of β-lactams and β-lactamase-inhibitors have been developed to counteract this mechanism. The application of these substances requires differentiated microbiological diagnostics and should be embedded in an interdisciplinary infection management.

Conflicts of interest

The author declares no competing interests.

Keywords

Gram-negative Bacterial Infections – Beta-lactam Resistance – Beta-lactamases – β-lactamase Inhibitors

Introduction

The use of antibiotics is a therapeutic measure of daily routine in human medicine. Prevalence studies revealed that approx. 20–30 % of the patients treated in normal wards receive antibiotics, whereas prescription rates of 50 % and more are usually registered at ICUs [1]. These figures illustrate that the efficiency of modern medicine depends to a relevant degree on the availability of effective anti-infective drugs. Unfortunately, the progressive **development of resistances** is leading to an insidious loss of efficacy of numerous antibiotics. Today, there are many situations of empirical initial therapy in which substances are applied which were classified as **antibiotics of last resort** just a few years ago and have been very selectively prescribed. [2]. Such a development inevitably results in the induction of resistance to these substances. Apart from measures designed to improve the administration of antibiotics and reduce the spread of resistance (hospital hygiene), new antibiotics are therefore needed in order to remain capable of action in daily routine [3].

This article will first focus on the current development of resistance and the resulting therapeutic challenges. Then the state of development of new antibiotics will be described, specifically discussing several of the new substances. The focus is set on antibiotics acting against Gram-negative microbial pathogens. Finally, proposals on how to embed new antibiotics in rational infection management will be discussed.

Development of resistance

General aspects of resistance development

The phenomenon of bacterial resistance to antibiotically active substances is a process of natural development which has not been induced by human civilization [4]. Yet there is no doubt that the use of antibiotics by humanity has a cru-

cial impact on the speed and dimension of resistance development [5]. While the exposure to antibiotics produces an **evolutionary selection pressure** on resistant bacterial clones, a number of other factors contribute to the spread of resistant microbial pathogens. Foremost, the

- transmission in a nosocomial environment,
- acquisition by long-distance travel to certain world regions, and
- contact with the natural environment (water bodies, food, animals)

must be mentioned in this regard [6,7].

Certain microbial pathogens are problematic as far as their development of resistance is concerned. Resistances to various substance classes often appear in combination, which is typically referred to as multi-resistance. At present, there is unfortunately no commonly used terminology to unambiguously classify such microbial pathogens. The MRGN classification for Gram-negative bacteria commonly used in Germany provides an orientation that can be used for epidemiological purposes and to guide hospital hygiene measures [8].

In the Gram-positive spectrum, isolates of **Staphylococcus aureus** with resistance to methicillin (MRSA) and **Enterococcus faecium** with resistance to vancomycin (VRE) are typical examples of problematic germs. However, Gram-negative pathogens are affected to a far greater extent, whereby Enterobacteriaceae (e.g. **Escherichia coli, Klebsiella spp.**, etc.) as well as non-fermenting bacteria (e.g. **Pseudomonas aeruginosa**, **Acinetobacter baumanii**, etc.) are of significance. The resistance problem is genetically and epidemiologically distinctly more heterogeneous and complex in the Gram-negative spectrum [9] as this is the case with MRSA and VRE.

Multiresistant pathogens are not more dangerous or virulent than their respective wildtypes which are tested as susceptible to a larger number of antibiotics. However, therapy is more difficult because the choice of substances is limited.

In particular situations only **reserve compounds** are available, which may have many side effects (e.g. nephrotoxicity of colistin in combination with aminoglycosides). In addition, the calculated therapy in case of multiresistant pathogens is more often inadequate, which might be associated with a worse outcome.

The epidemiological developments of resistant pathogens vary and are pathogen-specific [10]. For example, a decline of MRSA rates can be observed in many countries, whereas increasing case numbers with VRE [11] and Gram-negative pathogens [12] are identified. The pathogen species also display huge differences, which makes generalised statements on the resistance epidemiology difficult. In general, the situation in Germany is currently better than in a few neighbouring European countries [13]. A current overview of the resistance situation on national and/or regional level can be queried on the web site of the **Antibiotic Resistance Surveillance (ARS) Network** of the Robert Koch Institute (https://ars.rki.de/). Irrespective of this (particularly for clinical decisions!), the **local resistance statistics** must be taken into regard, which, according to the Infection Protection Act, needs to be provided by each hospital.

Resistance to β-lactam antibiotics – a central problem

Penicillins, cephalosporins, monobactams (aztreonam) and carbapenems belong to the group of the β-lactam **antibiotics** and represent a class of antibiotics very often applied. The advantages of this substance group are their

- low specific toxicity,
- very broad activity spectrum, and
- good tissue penetration in various compartments.

One essential **resistance mechanism** against β-lactams is their enzymatic inactivation by bacterial enzymes, the so-called **β-lactamases** [9]. This umbrella term covers a great number of different enzymes, e.g. penicillinases, cephalosporinases and carbapenemases. Unfortunately, these designations do not always permit drawing conclusions on the potential substrates of the β-lactamases. However, a common feature of these enzymes is their mechanism of action. By opening the ß-lactam ring of the antibiotic molecules, the latter can no longer bind to penicillin-binding proteins and thus lose their antibacterial effect.

Apart from the enzymatic inactivation, resistance to β-lactam antibiotics can also be induced by other mechanisms, for example, by modifications of **penicillin-binding proteins**, **porin loss** or **efflux pumps**. In the latter two mechanisms mentioned, the diffusion of the molecule to its target site is hampered by the absence of pores in the cell membrane and/or an oppositely directed transport mechanism is at work [9]. In unfavourable cases, various resistance mechanisms might exist concomitantly, which is not necessarily directly visible in a resistogram (phenotype).

In a simplified view of the problem of β-lactam resistance two essential categories can be distinguished:

- Firstly, there are pathogens which are **resistant to third-generation cephalosporins** (and often to piperacillin/tazobactam). In this case, carbapenems are effective and therefore they are being more often applied. Gram-negative pathogens possessing this constellation of resistance are increasingly discovered all over the world [12], which harbours the risk of an accelerated induction of resistance to carbapenems [2].
- Apart from this constellation, the phenomenon of **carbapenem resistance** among Gram-negative pathogens deserves special consideration. All β-lactams are often ineffective in this situation and additional resistances to other substance groups, e.g. the quinolones, are often found. The therapeutic options are reduced to a few antibiotics, which are once again associated with substance-specific disadvantages (e.g. nephrotoxicity due to colistin and aminoglycosides).

β-Lactamases – a frequent mechanism of resistance

There is an almost unmanageable variety of different β-lactamases which are found especially in Gram-negative pathogens. Beyond this, the circumstance that genes encoding the resistance mechanisms are often located in **plasmids** (extrachromosomal DNA), which can be easily exchanged in bacterial cells. This phenomenon plays a role in the propagation of antibiotic resistances both between pathogens of one species or even across the boundaries of species.

β-lactamases can be can be classified either according to the **Ambler Classification** or the **Bush-Jacoby-Medeiros Classification** [14,15]. While the classification according to Ambler depends on the amino sequence of the enzymes, the classification according to Bush-Jacoby-Medeiros attempts to establish a functional differentiation of the β-lactamases considering both substrates and inhibitors. However, the use of both classification systems in (clinical) everyday routine is not very widespread. Firstly, the fundamental molecular biology is complicated, secondly, only few microbiological laboratories are specialised to differentiate β-lactamases and report the results back to the requesting clinician in good time. Since the therapy of infections depends mostly on **phenotypic susceptibility testing** of antibiotics, looking at the underlying molecular biology seems to be somewhat unnecessary and cumbersome at first. However, this should not obscure the fact that resistance epidemiology and new antibiotics will include these aspects in bedside considerations. It may therefore be expected in the medium term that a detailed testing of resistance mechanisms against β-lactams will be introduced into the routine spectrum of microbiological testing. This diagnostic approach will become more and more relevant especially owing to the increasing availability of β-lactamase inhibitors (see below).

The **inhibition of β-lactamases** has been a concept commonly used in antibiotic therapy for many years [14,15]. The efficacy of an antibiotic can be restored by the co-administration of a β-lactamase inhibitor (BLI). Well known and often applied are the combinations of ampicillin/sulbactam, amoxicillin/clavulanic acid and piperacillin/tazobactam.

The problem of developing new antibiotics

General considerations

For many years, the development of resistances, observed ever since antibiotics have been clinically used, has not been much of a problem, because new treatment options have been made available on a regular basis by the new development of antibiotics. Only in the last ca. 10 to 15 years did a "drying up of the pipeline" become apparent and noticeable as a problem. For economic reasons, many pharmaceutical enterprises have terminated their commitment in the sector of anti-infectives, which is especially reflected by a deficiency of innovative mechanisms of action [16–18].

Against the backdrop of this development various political initiatives were launched in the past years which turned the problem of resistance development into a subject of international discussion [19]. One result of these activities was also a statement of the World Health Organization (WHO) on the **prioritisation of antibiotic development** (Tab. 1) [20]. Here, the great need for antibiotics effective against Gram-negative pathogens becomes clearly visible, in particular to overcome resistance to carbapenem. It must also be stated at this point that there is an urgent need for new treatment options against resistant tuberculosis bacteria. However, this problem is of a different nature and therefore shall not be further subject of this article.

On closer inspection, the "pipeline" of antibiotic development is not yet completely empty, instead, it still delivers new products on a low level. The problem is rather the insufficient amount of innovations and the absence of substances displaying novel mechanisms of action [19,21]. Many of the substances introduced to the market in the past years are **modifications of already available medicinal drugs or combinations of β-lactams with β-lactamase inhibitors** (BL/BLI). These combinations to some extent contain new molecules, however, the fundamental treatment strategy follows more traditional lines. The innovations consequently take place mainly in niches, where new options are available in special resistance constellations.

Tabl. 1

Priority list of the WHO for the development of new antibiotics (except tuberculosis). Pathogens with critical, high and moderate requirement of new treatment options are listed in descending order.

Priority 1: Requirement is ("critical")
• **Acinetobacter baumanii** with resistance to carbapenems
• **Pseudomonas aeruginosa** with resistance to carbapenems
• **Enterobacteriaceae** with resistance to carbapenems and third-generation cephalosporins
Priority 2: Requirement is "high"
• **Enterococcus faecium** with resistance to vancomycin
• **Staphylococcus aureus** with resistance to methicillin and/or vancomycin
• **Helicobacter pylori** with resistance to clarithromycin
• **Salmonella spp.** with resistance to fluoroquinolones
• **Neisseria gonorrhoeae** with resistance to fluoroquinolones and third-generation cephalosporins
Priority 3: Requirement is "moderate"
• **Streptococcus pneumoniae** with resistance to penicillin
• **Haemophilus influenzae** with resistance to ampicillin
• **Shigellas** with resistance to fluoroquinolones

New antibiotics against Gram-negative pathogens

A number of substances designed to treat diseases caused by Gram-negative pathogens have been put on the market in recent years. In the following, I will discuss the BL/BLI combinations consisting of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, the aminoglycoside plazomicin and the siderophore cephalosporin cefiderocol.

Ceftolozane/Tazobactam

Ceftolozane is a modification of the third-generation cephalosporin **ceftazidime**, which has been combined with the BLI **tazobactam** and is available under the trade name of **Zerbaxa®**. Ceftolozane has a better efficacy against **pseudomonas** which, for one reason, is due to a lower affinity to efflux pumps. This resistance mechanism is not unusual in Pseudomonas. The combination with tazobactam pursues the objective of protecting ceftolozane from some typical broad-spectrum β-lactamases. Ceftolozane/tazobactam is not effective in the presence of carbapenemases, which limits the therapeutic options of the drug [22]. The substance was initially examined in the context of marketing authorisation studies, in cases of urinary tract infections and (in combination with metronidazole) intraabdominal infections. By now, data are available for the therapy of other, mainly nosocomial infections [23–25]. In particular, nosocomial pneumonias have also been investigated in the meantime and the market authorisation of the drug has been extended by this indication.

Due to its action spectrum, ceftolozane/tazobactam can contribute to **lowering the use of carbapenem**. Considering the costs for therapy, however, it seems rather unlikely that many hospitals will routinely apply the substance for this indication. A possible indication for the application of ceftolozane/tazobactam will consist in the therapy of pseudomonas infections if the isolate is susceptible. This also applies to the multiresistant isolates of this species, however, they must not possess a carbapenemase. If these conditions are fulfilled, ceftolozane/tazobactam might be an alternative to colistin and aminoglycosides [24].

Ceftazidime/Avibactam

A combination of the pseudomonas-effective, third-generation cephalosporin **ceftazidime** with the new BLI **avibactam** is available under the trade names of **Avycaz®** (USA) and **Zavicefta®** (Europe). Avibactam protects ceftazidime from being inactivated by a great variety of β-lactamases belonging to Ambler classes A and C as well as some members of class B. A special feature is the inhibition of several carbapenemases of the KPC (Klebsiella pneumoniae carbapenemase) type as well as some OXA (oxacillinase) carbapenemases. According to current opinion, this is the special clinical application area for the substance. Ceftazidime/avibactam was tested in cases of complicated urinary tract infections and (in combination with metronidazole) complicated intraabdominal infections in the scope of marketing authorisation studies. By now, study results are also available for nosocomial pneumonias [26]. Compared to the tested reference substances (often carbapenems), ceftazidime/avibactam had similar efficacy rates, however, they were associated with a higher frequency of side effects which the study ascribed to this substance [27].

Meropenem/Vaborbactam

The combination of the carbapenem **meropenem** with the boric acid derivative **vaborbactam** acting as a β-lactamase inhibitor is available under the trade name **Vabomere®**. It has a marketing authorisation for the indications of complicated urinary tract infections, intraabdominal infections and nosocomial pneumonias. The combination with vaborbactam protects meropenem from be inactivated by carbapenemases of the KPC type [28,29]. Other β-lactamases inhibited by vaborbactam are not of significance in this combination, as meropenem will not be inactivated by many of them, even if the inhibitor is absent. As far as meropenem/vaborbactam is concerned, it is worth mentioning the TANGO-2 study in which the substance was applied to carbapenem-resistant pathogens and then compared with various other antibiotics [30]. In this setting, which is much closer to the product's actual field of application from a clinical perspective than the other marketing authorization studies, meropenem/vaborbactam produced a higher healing rate and less side effects than the prescribed reference substances.

Imipenem/Relebactam

The BL/BLI combination of **imipenem** and **relebactam (Recarbrio®)** has a spectrum very similar to that of meropenem/vaborbactam [28]. As is the case with the known imipenem, imipenem/relebactam also contains **cilastatin** as an inhibitor of dehydropeptidase-1. Relebactam protects imipenem particularly from inactivation due to carbapenemases of the KPC type. In mid-2021, imipenem/relebactam received a marketing authorisation in our country for nosocomial and ventilation-associated pneumonias [31] as well as (Gram-negative) pathogens with limited therapy options [32].

Plazomicin

Aminoglycosides are still being regularly applied as combination partners, especially in the therapy of multiresistant Gram-negative pathogens. However, the **nephrotoxicity** of the substance and the **development of resistance**, which is particularly due to the expression of aminoglycoside-modifying enzymes, still present a problem. Unfortunately, resistances to β-lactams and aminoglycosides also occur in combination, which limits the application options.

The substance **plazomicin (Zemdri®)** was approved in the USA for the treatment of complicated urinary tract infections caused by Gram-negative pathogens. Multiple modifications of its molecular structure make plazomicin resistant to some of the most important types of aminoglycoside-modifying enzymes, which often occur in β-lactam-resistant pathogens [33]. This makes plazomicin

appear to be an interesting therapeutic alternative in this situation. The most (published) experience made so far comes from the therapy of urinary tract infections in which the product displayed good clinical results when used as a monotherapy, which particularly also comprised pathogens with carbapenem resistance [34]. According to current opinion, this seems to be a preferential field of plazomicin application. As far as systemic infections are concerned, it remains to be seen what status this antibiotic will reach. A monotherapy outside the urinary tract seems quite unlikely, for which reason plazomicin may be expected to be applied as a combination partner in these situations. In the summer of 2000, the manufacturing company stopped the marketing authorisation process in Europe for economic reasons, whereas plazomicin is still available in the USA. At present, any further development is therefore uncertain.

Cefiderocol

Cefiderocol (USA: **Fetroja®**; Europe: **Fetcroja®**) is a novel cephalosporin, which has some similar features in common with ceftazidime and cefepime [35]. As an innovative mechanism of action, the molecule has a catechol group which acts as a siderophore and binds extracellular iron in chelate complex. With the aid of bacterial iron transporters, the siderophore group enables cefiderocol to travel into the periplasmic space of the Gram-negative pathogens, where it inhibits penicillin-binding proteins. This transport mechanism mediates the efficacy of cefiderocol against numerous pathogens in which **efflux pumps** and **porin loss** occur as the mechanisms of resistance. A hitherto unique feature of the substance is its **non-susceptibility to metallo-β-lactamases**, enzymes which are not inhibited by the other BL/BLI combinations here described. Apart from ceftazidime/avibactam, cefiderocol is also the second, clinically available new substance showing effects against carbapenemases of the OXA-48 type. In a direct comparison with a high-dosed meropenem therapy (3x 2g as prolonged infusion) cefiderocol was not seen to be inferior in the treatment of nosocomial pneumonias, without expressly focusing on multiresistant pathogens [36].

Application of new antibiotics – many challenges

The clinical use of new antibiotics is associated with a number of problems. One very obvious aspect is the high **price of the medicinal products**. Given the costs for therapy, which range between approx. € 100 and € 500, their broad application will not proceed as first-line therapy. However, this circumstance is rather advantageous, since an uncontrolled prescription must be prevented for microbiological/epidemiological reasons.

The greatest challenge of the new substances is **determining their indications**. It proves difficult to define the situations in which products can be prescribed with calculation. In case of infections in which ceftolozane/tazobactam and ceftazidime/avibactam are safely effective (e.g. when expecting Enterobacteriaceae with a formation of broad-spectrum beta-lactamases of the ESBL type), one would routinely rather resort to a carbapenem. Even if reducing carbapenem administrations were desirable, the application of antibiotics which cost many times more would hardly be justifiable in this situation. There is also the question whether the new products might not be too valuable because of their specific efficacies just to be "burned" as mere carbapenem replacements.

With a view to the specific efficacies of the substances, which accounts for their actual worth, the situation is much more complex. Since resistances to β-lactams might be induced by a variety of different mechanisms, it will be almost impossible in hospital routine to make a calculated decision on the constellation one is dealing with in a concrete case of infection. As most of the new substances address only partial aspects of a heterogeneous resistance problem, there is a risk of inadequate therapy when these new substances are applied in a calculated manner.

According to current opinion, a broad empiric therapy with cefiderocol will most likely come into question because of its action spectrum and being non-susceptible to a great many of β-lactamases (incl. diverse carbapenemases) and also because it remains effective in case of porin loss and efflux.

Nevertheless, a pragmatic categorisation of most new antibiotics based on "if-then" algorithms (e.g. meropenem/vaborbactam works always in case of resistance to carbapenems) is not possible without further ado. It thus follows that **susceptibility testing** is needed for the new products. This poses major challenges for microbiological laboratories. Apart from establishing the technical test requirements, it must be determined in which situations the new substances are to be tested. As broad-based routine susceptibility testing does not appear to be reasonable, the decision will probably depend on the **resistance pattern of the pathogen** and will have to be demand-oriented. However, this will cause a delay which will not permit a timely application of the respective substance and thus have an impact on the treatment result.

Decisions on which of new antibiotics may be useful in clinical routine must invariably include the prevailing **local or regional resistance situation**.

Since the molecular resistance epidemiology varies among hospitals, it is not possible to determine universally which new antibiotic will reinforce the therapeutic armamentarium.

This applies particularly to the BL/BLI substances. The occurrence of β-lactamases and the resulting inhibition possibilities are very variable [37–39]. Products showing a very good efficacy in one region might prove to a greater extent to be ineffective in another in

which other resistance mechanisms may be clonally distributed. In addition to the individual consultation with the microbiological laboratory, the National Reference Center (NRZ) for Gram-negative pathogens in Bochum, Germany (http://memiserf.medmikro.ruhr-uni-bochum.de/nrz/) provides Surveillance Reports on Prevalences in regular intervals [40].

Unfortunately, the currently available new antibiotics have typically not been tested and approved explicitly for the situations in which their actual significance lies. It is hardly possible in the scope of marketing authorisation studies to specifically select pathogens for which one product might represent a special treatment alternative. In addition, marketing authorisations often comprise, at least initially, only limited indications (e.g. urinary tract infections and intraabdominal infections). The application in cases of pneumonia then already means for some products an application outside the range of marketing authorisation, a circumstance which at least needs to be observed.

The status "new" pertaining to an antibiotic must not obscure the fact that the risk of resistance development exists for these substances as well [41]. This results in the necessity of not applying these valuable supplements to the therapeutic spectrum in an uncontrolled manner. As with many novel drug products, only clinical use will provide information about the benefits and problems of antibiotics.

Perspectives

Despite an existing deficiency of new developments, it may be expected that single new substances will become available for clinical therapy in the years to come. These will be, for example, additional **BL/BLI combinations** and further developed **fluoroquinolones** and **tetracyclines**, to some extent we may hope for the introduction **new mechanisms of action** [42]. It remains to be seen whether **β-lactamase inhibitors** will be available as **single substances** in the future or whether they are exclusively offered in fixed combinations with β-lactam-antibiotics. One advantage of separate BLI would be the option to combine them according to need and local epidemiology and thus expand their efficacy. Separating the BLI from β-lactam allow for a more differentiated dose adjustment of the antibiotic. However, in this case, a reasonable adjustment of the pharmacological properties of the BLI to their respective combination partners must be provided for (e.g. half-lives) which, in turn, will create new challenges. To decrease the problems associated with the new development of antibiotics, there are various starting points to make the respective activities more attractive [43]. It remains to be seen whether modified remuneration rules and research investments are able to create sufficient incentives to support antibiotic development.

The availability of new antibiotics is a challenge to clinical routine which needs to be taken seriously, as microbiological aspects (resistance mechanisms, epidemiology) need to be dealt with in a much more differentiated manner. Probably these hurdles can only be taken if infection management receives **interdisciplinary support**. It consequently makes sense to regulate the application of new antibiotics and install preceding differentiated consultancy in such cases. Ideally, this can take place in the scope of an **Antibiotic Stewardship Programme**, where bundling of competences from infectiology, microbiology and pharmaceutics will be made possible [44]. Irrespective of this, the most important step in slowing down the development of resistance is to **optimise antibiotic use**, which can be achieved by the implementation of Antibiotic Stewardship Programmes.

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Corresponding author

Dr. med.
Christian Lanckohr, EDIC

Antibiotic Stewardship (ABS)-Team
Institute for Hygiene
University Clinic Münster
Robert-Koch-Straße 41
48149 Münster, Germany

Phone: +49 (0) 251 83-44058

E-Mail:
christian.lanckohr@ukmuenster.de

ORCID-ID: 0000-0003-2822-8122