APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

APMIS 127: 361–371

DOI 10.1111/apm.12951

REVIEW ARTICLE

Antibiotic therapy as personalized medicine – general considerations and complicating factors

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Moser C, Lerche CJ, Thomsen K, Hartvig T, Schierbeck J, Jensen PØ, Ciofu O, Høiby N. Antibiotic therapy as personalized medicine – general considerations and complicating factors. APMIS 2019;127:361–371.

The discovery of antibiotic drugs is considered one of the previous century's most important medical discoveries (Medicine's 10 greatest discoveries. New Haven, CT: Yale University Press, 1998: 263). Appropriate use of antibiotics saves millions of lives each year and prevents infectious complications for numerous people. Still, infections kill unacceptable many people around the world, even in developed countries with easy access to most antibiotic drugs. Optimal use of antibiotics is dependent on the identification of primary and secondary focus, and knowledge on which pathogens to expect in a specific infectious syndrome and information on general patterns of regional antibiotic resistance. Furthermore, sampling for microbiological analysis, knowledge of patient immune status and organ functions, travel history, pharmacokinetics and -dynamics of the different antibiotics and possible biofilm formation are among several factors involved in antibiotic therapy of infectious diseases. The present review aims at describing important considerations when using antibacterial antibiotics and to describe how this is becoming substantially more personalized. The parameters relevant in considering the optimal use of antibiotics to treat infections are shown in Fig. 1 – leading to the most relevant antibiotic therapy for that specific patient. To illustrate this subject, the present review's focus will be on challenges with optimal dosing of antibiotics and risks of underdosing. Especially, in cases highly challenging for achieving the aimed antibiotic effect against bacterial infections – this includes augmented renal clearance (ARC) in sepsis, dosing challenges of antibiotics in pregnancy and against biofilm infections.

Key words: Antibiotics; precision medicine; sepsis; augmented renal clearance; pharmacokinetics; pharmacodynamics; biofilm infections.

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GENERAL USE OF ANTIBIOTICS

The use of antibiotics provides the option for a targeted killing of infecting microorganisms, with minimal side effects on the host cells. All antibiotic therapies are based on an individual evaluation of the patients. In recent years, there has been an increasing focus on antibiotic resistance and antibiotic stewardship programs to prevent further antibiotic resistance. This is particularly important due to the lack of new classes of antibiotics. The antibiotic treatments can be divided into whether they are empiric treatment without guidance of microbiological analysis or definitive antibiotic therapy based on the identification of relevant bacterial etiologies and optionally *in vitro* susceptibility testing (1) (Fig. 1).

In addition, antibiotics can be used as prophylactic therapy included in cases of various surgical procedures or prevention of endocarditis during dental procedures. Antibiotic therapy can also be given as pre-emptive therapies in fragile patients like stem cell or solid organ transplanted patients with cytomegalovirus (CMV) in the blood, candida colonization in patients in the intensive care units (ICUs) or patients with cystic fibrosis (CF)

Received 20 March 2019. Accepted 7 April 2019

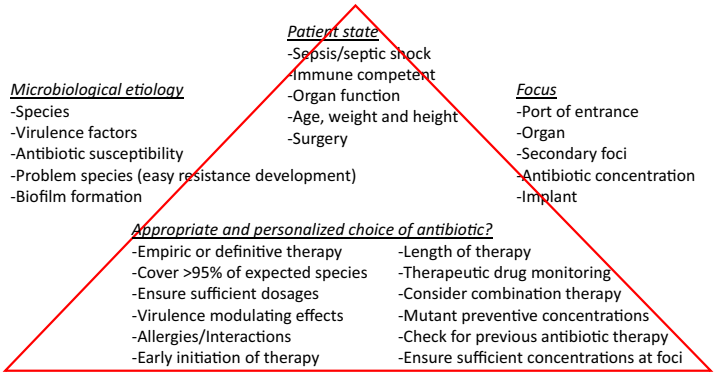

Fig. 1. The figure indicates the numerous factors, which have to be considered when using antibiotic therapy and dosing correctly. This shows why so many decisions on using antibiotic therapy end up as being personalized treatments.

intermittently colonized with *Pseudomonas aeruginosa* in the airways. These are antibiotic treatments based on the identification of microorganisms, without clinical symptoms of infection of the patients – the reason for pre-emptive antibiotic therapies is the risk that the colonization with a given microorganism often proceeds to actual infections with the same microorganism, which is difficult to eliminate (2–5).

In some cases, especially in patients with foreign body implants, where the implant cannot be removed or exchanged, chronic suppressive (sometimes lifelong) antibiotic therapy may be needed. The background for these treatments is the formation of microbial biofilms (see later) on the implants (4). Biofilms are formed with significantly increased tolerance to the antibiotics, and therefore impaired bacterial elimination and risk of regrowth when the antibiotic treatment is terminated (4,6).

DOSING OF ANTIBIOTICS

Infectious diseases, especially caused by bacteria or fungi, are characteristic in the way that it is possible to test the disease promoting pathogen (if known) for susceptibility to the several antibiotics, by means of *in vitro* susceptibility testing. This is, in most cases, performed by disk diffusion in the clinical microbiological laboratory under standardized conditions (Comparison of European Committee on Antimicrobial Susceptibility Testing (EUCAST)). In this way, the zone diameter (and thereby the bacterial minimal inhibitory concentration (MIC)) can be translated into a level of susceptibility using established breakpoints (susceptible, intermediate susceptible, resistant) to various antibiotic drugs and the treatment can be chosen from the results of these tests. The testing and the reported susceptibility pattern of the pathogen are depending on whether sufficient concentrations of the antibiotic can be obtained in the serum of the patients without unacceptable side effects or toxicity. The species of bacteria, which are susceptible to the antibiotic, is generally known as the spectrum of the antibiotic and is of course fundamental in antibiotic usage.

In general, most studies on pharmacokinetics (PK) have been performed in small groups constituted of persons who are normal in weight and height (Fig. 2) (7). Even in these studies, it is evident that there is a substantial interindividual variation in PK. In infected patients, the PK is further impacted by changed perfusion due to the inflammatory response. Previously, it has been an unspoken dogma that "one size fits all" when it comes to antibiotic dosing. However, studies have revealed that we are not achieving the serum concentrations expected by standard dosing (8). In a Thailand study investigating meropenem dosing in eight neutropenic patients with bloodstream infection, three meropenem dosing regimens were compared with the standard bolus infusion of 1 g of meropenem probability of target attainment (PTA) of 75% of the dosing interval above the breakpoint of 2 mg/L which would only be achieved in 22% of the patients (9). The PTA could be increased by elongating the infusion time and increasing the dosage (9). Comparable observations on significantly lower antibiotic concentrations than expected have also been reported for daptomycin and correlated to a poor outcome (10). Such studies strongly advocate against "one size fits all" and indicate needs for more individualized and thereby personalized antibiotic regimens (11,12). Besides not eradicating the infection, the low antibiotic doses, at sub-MIC levels, have the potential of inducing and selecting antibiotic resistance development (13–16).

TABLE 1. Concentrations of antibiotics in sweat and blood of six healthy persons

Drug	Dose (g)	C_{max} (μg/ml)/T (h) in[a]:			MIC_{90} (μg/ml) for[f]:	
		Blood	Axilla sweat	Forearm sweat	MSS	MRS
Benzylpenicillin	1.2	27/0.5 (9–44)	2.6, 2.1, 0.1[b]/0.5–2	1.5, 0.4[c]/0.5	0.03	0.03
Phenoxymethylpenicillin	1.2	8/1 (4.1–14)	0.4[d]/4	0	0.06	0.06
Cefuroxime	1.5	62/1 (40–113)	7.8[e]/0.5	3.1[e]/3	1–2	≥128
Ceftriaxone	2	372/1 (82–480)	8.9/0.5 (0.7–16.2)	2.5/0.5 (0.9–6.0)	4	≥128
Ceftazidime	2	360/1 (160–920)	28.4/0.5 (1.1–70)	11/2 (1.0–23)	4–8	≥128

[a] Mean peak concentration in serum or sweat (C_{max})/time after administration of drug. Ranges of C_{max} are given in parentheses.
[b] Three of six persons had measurable concentrations (all are listed) (lower limit of detection, 0.1 μg/ml).
[c] Two of six persons had measurable concentrations (both are listed) (lower limit of detection 0.1 μg/ml).
[d] One of six persons had a measurable concentration (shown) (lower limit of detection, 0.1 μg/ml).
[e] One of six persons had a measurable concentration (shown) (lower limit of detection, 0.4 μg/ml).
[f] MSS and MRS, methicillin-susceptible and methicillin-resistant staphylococci, respectively (data from reference 12).

Fig. 2. A single administration of β-lactam antibiotics in healthy volunteers. The table shows the substantial interperson variations obtained of antibiotic concentrations after a single intravenous (IV) administration (except for phenoxymethylpenicillin) of the different β-antibiotics. The variations must be expected to be even more pronounced when treating infected patients with changes in perfusion and organ functions and receiving additional drugs (7).

FREQUENCY OF DOSING

For several years, it has been known that the beneficial outcome for the patients, besides the antimicrobial spectrum, is highly depending on dosing of the antibiotics. For obtaining the optimal effect of the bacterial killing or inhibition of bacterial growth, the dosing should include knowledge on whether the antibacterial effect is predominantly dependent on time above the MIC, area-under-the-curve (AUC) above the MIC or the peak concentration above the MIC (17). Modern dosing regimens' recommendations actually take this into account by recommending frequent dosing (time-dependent killing), once-a-day dosing (primarily concentration-dependent) or often twice-a-day dosing (AUC above MIC killing). Mostly, the inappropriate dosing during impaired organ function occurs if the optimal antimicrobial effects are not involved in decisions on the dose reductions.

Pharmacokinetic studies of critically ill patients are mostly focusing on dose reductions due to impaired organ functions, whereas changed perfusion and volume of distribution have attracted less attention (8,18). A special problem due to strict exclusion and inclusion criteria is that randomized, controlled clinical studies have the risk of not representing the kind of patients, subsequently will be treated with the investigated drug on a daily basis without the trial criteria (19). Thus, only 13% of the 187 patients, treated with tigecycline out of protocol, could potentially have been randomized in the clinical study and the patients were significantly more ill as compared to the randomized patient (19).

The immune competence status of the patients is also important for the PK/PD. Preclinical studies have shown good effect of carbapenems, if the serum concentration was >MIC in 40% of the dosing interval, while in neutropenic patients (n = 60) this parameter was increased to >MIC in 75% of the dosing interval (20,21). Likewise, for cephalosporins, where the serum concentrations >MIC in 60–70% of the dosing interval seemed appropriate. Subsequent studies, however, showed that the serum concentrations had to be >MIC in the entire dosing interval in 76 critically ill patients (22,23). When treating invasive *S. aureus* infections in 186 patients, dicloxacillin dosing at 1 g × 4 resulted in a significantly reduced mortality and relapse rate, as compared to a dosing with 1 g × 3 (24). The effect of fluoroquinolones is similarly increased significantly from a low AUC_{0-24}/MIC 30–100 to ≥125 and further up to >250 in a survey of 178 patients with enterobacteriaceae bacteremia (25). Using antibiotics, administered only once every 24 h, and where only one active antibiotic drug is provided, the C_{max} or the time, where the antibiotic dosing is >MIC becomes critically low, for example for ertapenem, ceftriaxone, aminoglycosides or for moxifloxacin. It is also important to obtain serum concentrations, resulting in sufficient concentrations in the primary infectious focus for the bacteremia and not only in the bloodstream. In the case of ARC with more than a 100% increase of renal clearance rate, it is important to be aware that necessary dose escalation can be substantial.

TIMING OF INITIATION OF ANTIBIOTIC THERAPY

Early control of infection is essential for the outcome. This is especially important for serious infections inducing septic shock (and severe sepsis with the former definitions). The earlier effective

antibiotic therapy is initiated, the better the chance is for a beneficial outcome, highly elegantly demonstrated by Kumar and colleagues on 2700 ICU patients (26), and later confirmed by others in similar evaluations on patients with severe sepsis or septic shock (27) (Fig. 3). The studies estimate an increase in mortality of 5–10% per hour, until appropriate antibiotic therapy is initiated. However, timing is also essential in cases inducing sepsis without shock, since the situation is not stable. If control is not obtained by appropriate antibiotic usage, the infection and the sepsis can proceed to more severe conditions with a significant increase in risk of fatal outcome from 10% to above 40% (28). Moreover, based on the evaluation of patients infected with various pathogens with different acquired resistance mechanisms, it has been revealed that the numbers needed to treat to save one patient were only five patients – in other words, it has been shown that the beneficial patient outcomes increase relatively easily by improving the frequencies of appropriate antibiotic regimens (29). The highest risk of poor outcome was associated with inefficient non-covering antibiotic therapy. In contrast, a systematic review and meta-analysis failed in identifying a significant mortality benefit of administering antibiotics within 3 h of emergency department triage or within 1 hour of shock recognition (30). However, and in contrast to the previously indicated studies, this review and meta-analysis did limit their study to whether the provided antibiotics were appropriate or effective, which is of course highly important – the antibiotics must be effective against the infecting microorganisms.

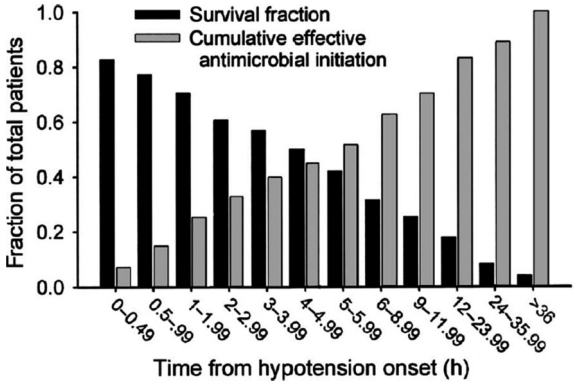

Fig. 3. The black bars in the figure show the fraction of surviving ICU patients in cohorts after initiation of a septic shock (hypotension) and the gray bars show the fraction of the same patients who have been administered effective antibiotic therapy. As can be seen from this retrospective survey of more than 2700 intensive care unit (ICU) patients, it is mandatory to initiate appropriate antibiotic therapy as early as possible (26).

FOCUS ATTAINMENT

All infections must have a port of entry. The urinary tract, the airways, the skin and the gastrointestinal tract are the most frequent primary foci. Fortunately, most infections are cleared at the port of entry, before systemic spread, although symptoms of the infection can be related to both localized signs of inflammation, but sometimes systemic signs of infection can be observed as well, like fever or sepsis. In any circumstance, even if systemic spread of the infection is the case, the primary focus must be eliminated, and this means the antibiotic drug must be able to penetrate to the primary focus in sufficient concentrations to kill or inhibit the pathogenic bacteria – also known as 'the drug to the bug'. In accordance, a recent review underlined the importance of the distribution of azithromycin to the anatomical site of infection or the treatment of bacterial sexually transmitted diseases (31).

AUGMENTED RENAL CLEARANCE

Early signs of sepsis are vasodilatation, capillary leakage and initially increased cardiac output. The result is the loss of liquid to the interstitial tissue and hypoalbuminemia with increased volume of distribution of hydrophilic antibiotics and reduced protein binding of antibiotics. Liquid therapy and vasoactive drugs lead to increased renal blood flow and augmented renal clearance (ARC) (32) (Fig. 4). The reduced protein binding leads to an increase in the free antibiotic concentration, however, the antibiotic concentration is reduced as a result of ARC. Primarily, the hydrophilic antibiotics like β-lactam- and carbapenem antibiotics, aminoglycosides and glycopeptides are affected. The ARC is being defined as a 24 h creatinine clearance (24 h CL_{Cr}) >130 mL/min/1.73 m^2 increasing to >300 mL/min (33).

The clinical consequences of ARC are somewhat less clarified. However, in a study of 93 critically ill patients reduced serum concentrations of vancomycin were revealed, despite the patients being treated by continuous drug infusion after an initial bolus dosing. The study showed a linear correlation between the 24t CL_{Cr} and the vancomycin concentrations. Only in 10% of the patients in the ARC group, the target attainment was achieved in the first 24 h (34). In another study, 81 patients were divided dependent on whether they fulfilled 2, 3 or

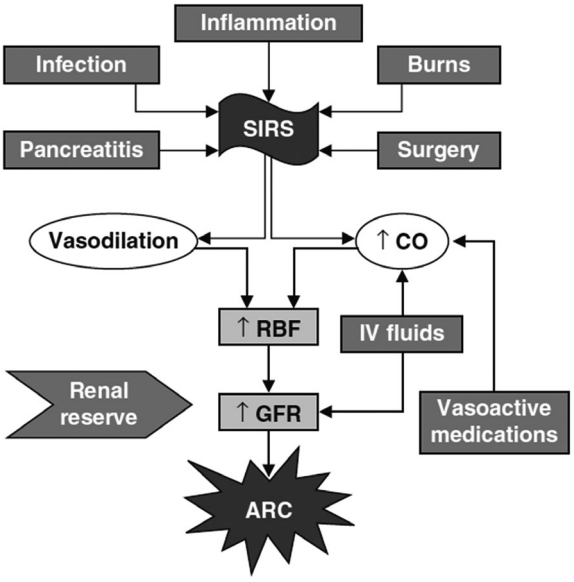

Fig. 4. A systemic inflammatory response results in important changes of elimination of hydrophilic antibiotic drugs. In addition to the changes shown in the figure, protein loss and reduced protein binding, edemas and increased volume of distribution add to the increased antibiotic elimination. If the creatinine clearance exceeds 130 mL/min/1.73 m^2, this is defined as augmented renal clearance (ARC). Lipophilic antibiotic drugs are not affected by ARC to a significant degree (32).

4 systemic inflammatory response syndrome (SIRS) criteria. The 24t CL_{Cr} and serum vancomycin "area-under-the-curve" (AUC)/MIC) were related to the SIRS criteria (35). Despite a significantly increasing 24 h CL_{Cr} 69% of the patients in the group, showing 4 SIRS criteria, did not achieve the AUC/MIC target of at least 400. These results show that the vancomycin concentrations achieved are substantially lower than the target attainments in cases of ARC. In addition, ARC have been shown to result in lower concentrations for β-lactam antibiotics. Population pharmacokinetics at a standard dosing of 1.5 g × 3 of cefuroxime for 20 critically ill patients and using a break point of 8 mg/L, an underdosing even at 24t CL_{Cr} 50 mL/min is revealed (36). Another study investigated a number of β-lactam antibiotic concentrations in critically ill patients at 50% and 100% of the dosing interval (8,37). Of the 248 critically ill patients included, who were treated for an infection, 16% did not achieve antibiotic concentrations >MIC in ≥50% of the dosing interval (37). Of these patients, one third had a poorer prognosis judged by their PK/PD results (37). Higher PK/PD ratio was associated with an improved outcome, especially if the concentration was >MIC in 100% of the dosing interval (37). In contrast, a study including 100 patients (64 with ARC) did not demonstrate a relation between the ARC and failure of antibiotic therapy (38). However, infection was only documented in 48% of the cases, the patients were not divided in relation to the severity of sepsis and the ARC patients had lower co-morbidity and Acute Physiology and Chronic Health Evaluation (APACHE) score (38).

Important are also substantial variations in the individual serum concentrations (7). Serum concentrations in relation to the MICs varied up to thousand times and for several of the drugs, the concentrations <MIC (37). Piperacillin-Tazobactam dosing of 4.5 g × 4 has also been shown not to provide sufficient concentrations in 16 out of 48 patients due to ARC (39). Two cases describing meropenem dosings state that dosing of 2 g × 6 and 2 g × 4 per 24 h, respectively, was necessary to obtain sufficient antibiotic levels and clinical effect (40). In a study including 71 critically ill patients (43 with sepsis and 28 multitrauma patients), they found that younger men with lower APACHE (Acute Physiology and Chronic Health Evaluation) II and SOFA (Sequential Organ Failure Assessment) score, and increased *cardiac output,* had increased risk for developing ARC (41). Whether a staging of the patients due to risk factors for ARC is useful on a daily basis is less likely due to the substantial variation in serum concentrations and overlap between the groups (41).

SPECIAL SITUATION, PREGNANCY

In a situation where sepsis is developing in a pregnant woman, close to her term, dosing of antibiotics is complicated, since the fetus and the amniotic fluid constitute a special pharmacokinetic compartment, where it is difficult to obtain sufficient antibiotic concentrations (Fig. 5) (42–44).

A pregnant woman at term has an approximately 4–5 L extra fluid in connection with the fetus depending on the weight of the fetus and the volume of distribution for the pregnant woman – for a cephalosporin antibiotic, this is increased from 7 to 12 L and the glomerular filtration rate (GRF) is increased with 50% already from the first trimester and continues to increase until the 37th week (42,45). Since most infections involving the fetus in pregnant woman ascend from the vagina through the cervix *'mucus plug'* to the amniotic fluid and from there to the fetus and through the amniotic film to the uterine tissue (44,46), the antibiotic therapy has to ensure sufficient concentrations rapidly in the amniotic fluid and the fetus and the uterine tissue (47). There is a concentration gradient from

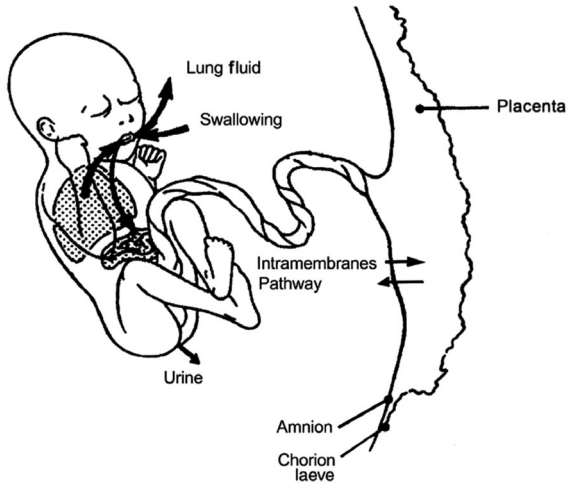

Fig. 5. Pregnancy results in a special situation for antibiotic dosing, especially if the fetus is affected. Please refer to text for details (45).

the pregnant woman's blood to the fetus and further to the amniotic fluid, which is predominantly (5/6) produced by the fetus urine and to a lesser degree from the fetus lungs (1/6) and close to the term to a minor degree from the uterus through the membrane (42,45). The amniotic fluid is equally removed by absorption over the amniotic membrane and by the fetus swallowing (45). Therefore, there is a delay, which increases in the case of hydroamnions, before sufficiently high antibiotic concentration is achieved in the amniotic fluid. Adequate PK/PD of aminoglycosides (concentration-dependent killing of bacteria) is highly difficult to obtain, while β-lactam antibiotics (time-dependent killing) can be achieved by high and frequent dosing (48). To obtain infectious control as early as possible, an extra dosing between the two first standard dosages of β-lactam- or carbapenem antibiotics can be administered.

SPECIAL SITUATION, BIOFILM INFECTIONS

In nature, disease bacteria and fungi live either as individual planktonic cells or as aggregates which may or may not adhere to surfaces – this is called biofilm growth (Fig. 6) (4). Generally, the planktonic lifestyle causes acute infections, which are susceptible to the host's innate and acquired defense mechanisms and to antibiotics, and they are therefore often easy to treat without major problems of recurrence or persistence. In contrast, biofilm infections are chronic and resistant to the host's defense systems and to antibiotics when conventional dosing is used. Furthermore, the defense mechanisms of the host aggravate the inflammation and cause chronic inflammation, which is the major cause of the tissue damage during biofilm infections. Biofilm infections are therefore characterized by recurrence or/and persistence of the symptoms, and sometimes they are the focus of systemic spread of the infections e.g. to the blood after a course of antibiotic treatment (4). When bacteria – or fungi – are isolated from biofilms, the routine antibiotic susceptibility testing is done with planktonically growing bacteria either by disk diffusion (EUCAST) or by broth dilution methods. In both cases, the estimated MIC, which is reported as Susceptible, Intermediate or Resistant based on established breakpoints, reflects planktonic bacteria giving rise to acute infections where they are predictive of therapeutic success or failure. This is not the case when the bacteria are growing as biofilms (4,49). The reason is that biofilm growing bacteria are tolerant to the dosages of antibiotics given systemically and the obtained concentrations at the infectious site. Methods have been designed to test biofilm growing bacteria for antibiotic susceptibility *in vitro* such as the Calgary Biofilm device, where the bacteria are growing as biofilms on pegs in the lid of microtiter trays and subsequently exposed to various concentrations of antibiotics. Finally, the surviving bacteria – if any – are detected by subculture in another microtiter tray without antibiotics. The results can then be reported as the Minimal Biofilm Bactericidal Concentration of an antibiotic (1000-fold reduction of the number of bacteria – colony-forming unit (CFU) – when breaking the biofilm by e.g. sonication) or Minimal Biofilm Eradication Concentration (no growth of bacteria). Unfortunately, the predictive clinical value of this method – therapeutic success – has not been proven (4). The current situation is, therefore, that we do not have any reliable routine *in vitro* assay for testing the activity of antibiotic against biofilm growing bacteria. There are several reasons for the antibiotic tolerance of biofilm growing bacteria. Although the basic PK/PD rules of antibiotics against biofilm growing bacteria are similar to the rules for planktonically growing bacteria (50), a major problem is that only the bacteria located at the surface of the biofilms are metabolically active, whereas the center consists of dormant bacteria (51). It is already known for decades that slow growing bacteria require longer exposure of many antibiotics to be eliminated (52). Furthermore, the anaerobic conditions in the center of biofilms (53) mean that such antibiotics (β-lactams, aminoglycosides, fluoroquinolones) are less efficient because radical oxygen species, which are produced during bacterial metabolism, contribute to the bactericidal efficacy of

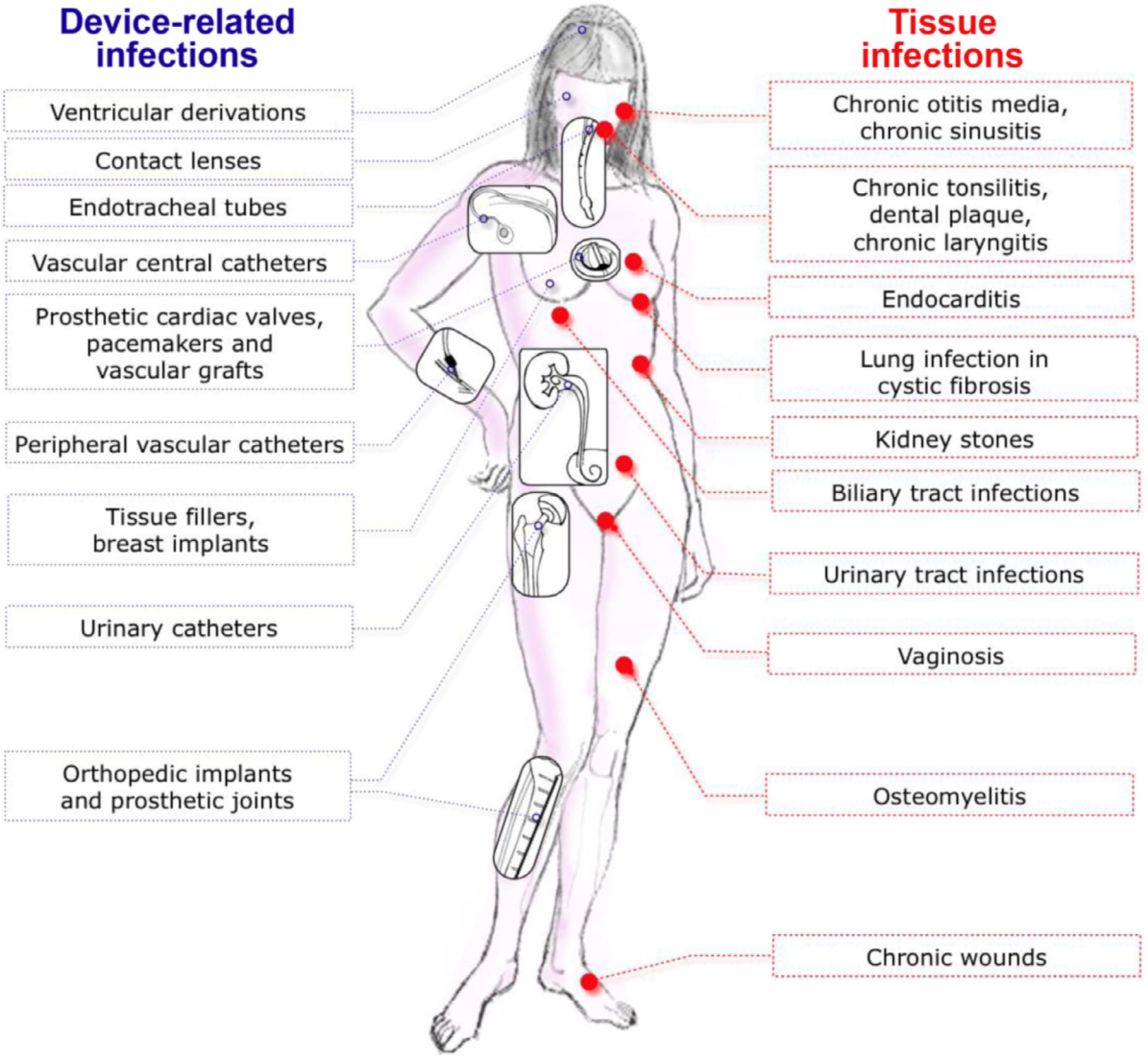

Fig. 6. The figure indicates how diverse and multifactorial biofilm-related infections are. Especially the distinction between foreign body and non-foreign body tissue related biofilms is important for handling the infections (4) (original in review by D. Lebeaux et al. Pathogens. 2013 May 13;2(2):288-356).

these antibiotics (54,55). This is not the case with colistin (56) and *in vitro* experiments using Confocal Laser Scanning Microscopy and Life-Dead staining have shown that e.g. combination of colistin and ciprofloxacin can kill a *P. aeruginosa* biofilm since the metabolically active surface of the biofilm is killed by ciprofloxacin (or tobramycin) and the dormant center of the biofilm is killed by colistin (57,58). Some antibiotics such as aminoglycosides are bound to the alginate matrix of *P. aeruginosa* biofilms and also to extracellular DNA and that interferes with the antibiotic action. Biofilms should, therefore, be considered as a third compartment when optimal dosing regimens are calculated (59,60). Since biofilms require much higher antibiotic concentrations and longer exposure time, efficient treatment in regard to elimination of infection, may not be possible with systemic administered antibiotics, but more efficiently treated with local or topical antibiotic administration. Most of the clinical experience and clinical trials on treatment of biofilm infections have been carried out in patients with cystic fibrosis (CF) and chronic *P. aeruginosa* biofilm lung infections (5). The experience from these patients is that it is possible to prevent chronic *P. aeruginosa* biofilm lung infection

by pre-emptive treatment of intermittent colonization of the lungs with inhalation with colistin and oral ciprofloxacin for 3 weeks (61). If the chronic biofilm infection is established, eradication is, in most cases, not possible. However, by using daily inhalation with colistin and daily oral azithromycin and, additionally, 2-week courses of intravenous antibiotics every 3 months it is possible to chronically suppress the biofilm infection and maintain the lung function for decades. This is called chronic biofilm suppressive therapy (62–64). These principles have been adapted for some other biofilm infection where it is not possible to eradicate the biofilms like non-replaceable vascular stents or orthopedic prosthesis and they are examples of personalized and precision medicine.

There are, fortunately, also biofilm infections where antibiotic prophylactics (65) and treatment are not so difficult e.g. endocarditis and successful antibiotic treatment can be obtained, even with orally administered antibiotics in stabilized patients after an initial intravenous course of appropriate antibiotic drugs (66,67).

THERAPEUTIC DRUG MONITORING

Therapeutic antibiotic concentration monitoring does not ensure that the initial dosing is sufficient and is most often only available for a few antibiotics (aminoglycosides, vancomycin and some antifungal drugs). In addition, the condition of critically ill patients can change rapidly resulting in needs for dose adjustments, which cannot await such measurements (8). The infecting microorganisms are usually not known at the time of initiation of antibiotics, and therefore it is not possible to adjust antibiotic dosing according to MIC values (68).

At present, the best procedure is to avoid antibiotic underdosing for critically ill patients suspected for an infectious disease, basically by dosing as high and frequently (continuous infusion) as possible. Combining antibiotics of different drug classes can also compensate for individual low concentrations of one of the antibiotics provided – like combining a hydrophilic with a lipophilic antibiotic. Most antibiotics have a high therapeutic index and for aminoglycosides, vancomycin and colistin, the risk of side effects is relatively low during the first few days of therapy – the same period where it is mandatory to obtain infectious control for a beneficial outcome. Dosages can be adjusted guided by concentration measurement and organ function monitoring. Therefore, a careful control of organ functions and the hyperdynamic phase is significant for monitoring the period, where the antibiotic dosing has to be increased, and when it may be necessary to reduce the dosing administered. Aminoglycoside dosing, where the total 24 h dosing is provided as one dose, was implemented to reduce nephrotoxicity, but actually meets the need for an increased initial dose. Similar strategy is used for colistin. Vancomycin can be dosed higher, than is usually recommended, and one can choose to provide an initial bolus (a "saturation" dose) to ensure sufficient antibiotic levels early on. Other possibilities to improve antibiotic dosing are continuous or prolonged infusions of β-lactam antibiotics and maybe also vancomycin (34,69,70).

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