Appendix A
Pitfalls of Antimicrobial Therapy in Prosthetic Joint Infection

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Abstract In this chapter, the peri- and post-operative monitoring of antibiotic therapy in infected total joint arthroplasty is presented from the clinical pharmacist's point of view. Recommendations for selection, risk factors, and monitoring are given.

The provision of clinical pharmacy service in infected total joint arthroplasty can be considered under a number of sections:

- Medicines reconciliation at every transition of care
- Perioperative medication management
- Monitoring of medical therapy
- Assuring in-patient and out-patient compliance during antimicrobial therapy

Keywords Antibiotics • Adverse events • Prevention • Rifampicin

Introduction

Periprosthetic joint infections are caused by microorganisms growing in biofilms, rendering these infections very difficult to diagnose and to eradicate. The treatment modalities differ from case to case, but always include antimicrobial therapy (Chap. 23). The current recommendations include 2 weeks of parenteral antibiotic treatment, followed by peroral antibiotics for overall duration of 3 months (6 months for knee prosthesis) [1, 2]. Most of the selected antimicrobial agents, especially

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rifampicin[1]-combination regimens, for treatment of periprosthetic joint infections are related with high incidence of adverse events. Especially the elderly patients are prone to hard-to-bear adverse drug events, which can lead to treatment failure. In this population, the adverse event rate is higher than that of younger adults due to the clinically significant changes in renal and hepatic function, and body composition associated with aging. Another important factor is the number of medications the elderly consume.

The optimal dosage regimen is also of clinical importance for effective antimicrobial therapy. High dosing is needed to achieve sufficient concentration in bone and surrounding tissues [1]. Taking into account the duration of antibiotic treatment, the adverse events are even more likely to occur.

Orthopedic surgeons frequently underestimate the impact of drug–drug and drug–disease interactions on negative results of antimicrobial treatment in these cases. It must be emphasized that most of the potential adverse drug events can be avoided with appropriate strategy, which includes medications reconciliation, drug therapy monitoring, and patient compliance assurance.

Polypharmacy in Orthopedic Surgical Patients

The majority of orthopedic patients undergoing primary total joint arthroplasty (TJA) are of age above 65, one-half of them older than 75, while revision total hip arthroplasty procedures were most commonly reported in the age group 75–84 [3–5]. Polypharmacy in the elderly is a common phenomenon secondary to the amount of medications required to treat the conditions that become more prevalent with age, such as heart disease, lung disease, metabolism problems, and diabetes. The presence of malignancy or systemic autoimmune disease such as rheumatoid arthritis also increases the incidence of polypharmacy [6]. In case of infected total joint arthroplasty, the introduction of antibiotic therapy, usually highly aggressive, can result in unexpected interactions with routinely used medications and lead to poor or negative outcomes. Patients with multiple medications, especially elderly, are at increased risk.

The potential interactions of routinely used medications with newly introduced antibiotic therapy can lead to two opposite situations: treatment failure because of decreased efficacy of antibiotic or, on the other hand, co-existing disease progression because of decreased efficacy of routinely used medications. Nevertheless, adverse drug events can significantly impact patient morbidity and mortality.

Dosing Regimen Impact

According to current concepts, long-term antibiotic treatment with high dose is needed to achieve treatment goals because of the biofilm resistance pattern. Generally the recommended antibiotics for treatment of infected total joint arthroplasty are not

[1] Rifampicin (INN) or rifampin (USAN) – vstaviti na dnu strani kot opombo!

officially approved for these indication, which is why the optimal dosing regimen in these cases is not established too. In most cases, the highest labeled dose of selected antibiotic (parenteral and peroral) approved for the most similar indication available is used for the treatment of prosthetic joint infections (PJI) (Chapter 23). However, the study results showed low cure rate when labeled dosing regimen was used for some antibiotics, especially rifampicin and co-trimoxazole [7–12]. Higher doses are needed. Current dosing regimens in contemporary clinical praxis are more or less empirical, without human pharmacokinetic/pharmacodynamics studies support. It must be emphasized that optimal dosing regimen, i.e., route of administration, dose and dosing interval of selected drug, is directly correlated to pharmacokinetic profile of a drug. In drugs with complex, nonlinear pharmacokinetic profile, narrow therapeutic index and significant intra-individual variability due to genetic polymorphisms of metabolizing enzymes, even slight changes in dosage regimen can result in decrease or loss of pharmacological effect and/or adverse events occurrence. Rifampicin has the most complex pharmacokinetic profile among antibiotics used in antimicrobial treatment of infected total joint arthroplasty.

The enormous inconsistency in dosing regimen is present for rifampicin, which has become the cornerstone for the treatment of infected PJI caused by *staphylococci*. According to published studies, the applied daily doses varied from 300 to 1,200 mg, as a single or subdivided doses [13–16]. On the other hand, the published evidence support only rifampicin doses of 450 mg twice daily to achieve high cure rate in combined antibiotic therapy [17]. It must be stressed that selected dosage regimen and duration of treatment strongly impacts on pharmacokinetics of rifampicin. A series of human studies indicate that daily dosages higher than 300–450 mg result in a more-than-proportional increase in both the peak concentrations of the drug and the area under the curve (AUC) in blood because of the saturation of efflux transport system through small intestine wall. The features of this effect differ if the same daily dose is administered as single dose or in subdivides doses. The daily fluctuation in serum concentration is more marked if higher doses are administered as single dose [18, 19]. It is of concern that during prolonged treatment rifampicin's bioavailability decreases from the excellent 93 % to only 68 % due to auto-induction of its own metabolism. Rifampicin's maximal auto-induction is reached in about 4 weeks [20, 21]. In the author's opinion, different dosage regimes can induce such fluctuations of serum concentration of rifampicin that therapeutic levels above MIC are not guaranteed for the entire 24-h time interval. It is very likely that this variability of serum concentrations is strongly dependent on rifampicin auto-induction mechanisms. Further studies are necessary to investigate dosage regimen impact on cure rate in these cases. Until clarification of this topic, the author endorses the use of rifampicin dosage regimen of 450 mg twice daily, supported by the only published randomized control trial (RCT), for combined antimicrobial treatment of PJI caused by *staphylococci*.

Note

- Caution is needed when using *off-label* dosing regimen especially in antibiotics with complex pharmacokinetic profile; the impact on kinetic pattern can lead to an unexpected decrease in efficacy of antibiotic treatment and increase of adverse event incidence.

The Role of Adverse Drug Interactions

In the broadest sense, a drug interaction occurs whenever one drug affects the pharmacokinetics, pharmacodynamics, efficacy, or toxicity of another drug. When the drug combination results in an undesired effect, the drug interaction becomes an adverse drug interaction.

Patients on antibiotic treatment of infected total joint arthroplasty, especially elderly, are highly exposed to adverse drug interactions because of their comorbidities and polypharmacy present. When high doses for prolong time are used, the incidence of adverse drug interactions is even higher. The question is which of them are clinically important? Readers should agree that clinically important adverse drug interactions which lead to adverse events that need treatment can negatively impact on patient compliance and contribute to poor treatment results.

With some simple calculations based on the reported magnitude of an interaction, it is possible to estimate the potential risk to a patient. Based on the degree of risk and the benefit of administering the drugs, the appropriate management options can then be selected [31].

Drug interactions of major clinical significance for antibiotics for infected PJI are listed in Table A.1 [22–30]. Of note is the fact that the beta-lactams rarely cause clinically significant drug–drug interactions.

Rifampicin

Among all antibiotics used for the treatment of infected joint replacements, rifampicin is the most problematic from the drug interaction point of view. Rifampicin is one of the strongest inducers of a number of drug-metabolizing enzymes, having the greatest effect on the expression of cytochrome P450 (CYP) in the liver and in the small intestine, among all drugs currently used. In addition, rifampicin induces some drug transporter proteins, such as intestinal and hepatic P-glycoprotein and MRP (multidrug-resistance protein). Full induction of drug-metabolizing enzymes is reached in about 1 week after starting rifampicin treatment and the induction dissipates in roughly 2 weeks after discontinuing rifampicin. Rifampicin has its greatest effects on the pharmacokinetics of orally administered drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 and/or are transported by P-glycoprotein and MRP [32, 33].

Thus, for example, oral midazolam, triazolam, simvastatin, verapamil, and most dihydropyridine calcium channel antagonists are ineffective during rifampicin treatment. The plasma concentrations of several anti-infectives, such as the antimycotics itraconazole and ketoconazole and the HIV protease inhibitors indinavir, nelfinavir, and saquinavir, are also greatly reduced by rifampicin. The use of rifampicin with these HIV protease inhibitors is contraindicated to avoid treatment failures. Rifampicin can cause acute transplant rejection in patients treated with

immunosuppressive drugs, such as cyclosporin. In addition, rifampicin reduces the plasma concentrations of methadone, leading to symptoms of opioid withdrawal in most patients. Rifampicin also induces CYP2C-mediated metabolism and thus reduces the plasma concentrations of, for example, the substrate (S)-warfarin and the sulfonylurea antidiabetic drugs. In addition, rifampicin can reduce the plasma concentrations of drugs that are not metabolized (e.g., digoxin) by inducing drug transporters such as P-glycoprotein. Thus, the effects of rifampicin on drug metabolism and transport are broad and of established clinical significance [34, 35].

The main concern is caused by substantial intra- and inter-individual pharmacokinetic variability due to the presence of gene polymorphism of drug influx and efflux transporter genes. These polymorphisms result in significant reduction in rifampicin AUC0-24. The presence of transporter gene polymorphisms is highly unpredictable and probably the reason of unexpected adverse drug interaction or treatment failure [36].

Potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment. It is particularly important to remember that the concentrations of many of the other drugs used by the patients will increase when rifampicin is discontinued as the induction starts to decrease!

Complementary and Alternative Medicines

Patients on antibiotic therapy are very likely to use complementary and alternative medicines (CAMs) in good faith of avoiding adverse event due to antibiotics and contribute to better treatment outcome. However, CAMs, i.e., glucosamine, chitosan, St. John's Worth, vitamins and minerals, CoQ10, therapeutic nutrition shakes, are related with potentially or confirmed serious interactions with prescription medicines concurrently taken [37]. We must take into account the unregulated nature of many CAM products and that the suspected mechanism of an interaction may not be what it appears. During antibiotic treatment, especially rifampicin-based, all CAMs should be avoided. Caution is also needed in the enterally fed patients because of increased incidence of diarrhea due to concomitant therapy with antibiotics [38]. Enteral feeding products also significantly decrease the absorption of quinolones, thus a particular attention must be put on correct dosing time between both [39].

Note

- The majority of adverse drug–drug and drug–disease interactions can be predicted.
- Half-lives of two interacting drugs are not good indicators to estimate the time required for induction onset and offset.
- Adverse drug interaction could result not only after drug introduction, but also after drug discontinuation.
- Drug interaction classification systems should be used only for general guidance! The individual patient risk factors and variables evaluation should always be the platform for decision on suitable course of action.

Table A.1 Antibiotics, used in infected TJA, drug interaction of major clinical significance

Antibiotic	Drug	Interaction type	Action
Rifampicin	Warfarin	Increased warfarin metabolism	Switch to LMWH[a]
	Dabigatran	Increased dabigatran efflux transport	Switch to LMWH
	Rivaroxaban	Increased rivaroxaban efflux transport and metabolism	Switch to LMWH
	Clopidrogel	Increased clopidrogel active metabolite production	Therapy monitoring or change therapy
	PPI[b]	Dose dependent induction of PPI metabolism (no clinical sign of pantoprazole metabolism induction)	Switch to pantoprazole
	Tamoxifen	Increased tamoxifen metabolism	Change therapy
	Cyclosporine	Increased cyclosporine metabolism	Change therapy
	Antiarrhytmics[c]	Increased antiarrhytmic metabolism	Change therapy; in case of amiodarone, increase dose and monitor efficacy
	Calcium channel blockers	Increased metabolism	Change therapy
	Azole antifungal agents[d]	Decrease concentration of azole antifungal agents	Avoid combination, change therapy
	Leflunomide	Increased serum concentrations of the active metabolite of leflunomide	Therapy monitoring or change therapy
	Benzodiazepines (metabolized by oxidation)	Increase the metabolism	Therapy monitoring or change therapy to lorazepam, oxazepam
	Boosted saquinavir	Significant hepatocellular toxicity	Avoid combination, change therapy
	Atazanavir	Decrease the serum concentration of atazanavir	Avoid combination, change therapy
	Oral contraceptives	Decreased contraceptive efficacy	Change to alternative method of contraception
	Food	Significantly decrease absorbtion	Only on empty stomach

Ciprofloxacin	Warfarin	Enhance the anticoagulant effect of warfarin	Therapy monitoring
	Antacides	Decrease the absorption	Correct dosing time or change therapy
	BCG	Diminish the therapeutic effect of BCG	Avoid combination
	Didanosine	Decrease the serum concentration	Use systemic route of administration of ciprofloxacin or change therapy
	Tizanidine	Increased concentration of tizanidine	Avoid combination
	Theophylline derivatives	Decrease the metabolism of theophylline derivatives	Therapy monitoring
	Cyclosporine	Increased concentration of cyclosporine	Therapy monitoring
	Phenitoin	Decrease concentration of phenitoin	Therapy monitoring
Minocyclin	Retinoic acid derivatives	Enhance the adverse/toxic effect of retinoic acid derivatives	Avoid combination
	Divalent or trivalent cation	Decrease the absorption	Correct dosing time or change therapy
Fusidic acid	Protease inhibitors	Decrease the metabolism of fusidic acid	Change therapy
Cotrimoxazole	Methotrexate	Enhance the adverse/toxic effect of methotrexate	Change therapy
	Warfarin	Enhance the anticoagulant effect of warfarin	Avoid combination
Gentamicin	Agalsidase alfa	Diminish the therapeutic effect of agalsidase alfa	Avoid combination
Imipenem/cilastatin	Ganciclovir	Increase risk of seizures	Avoid combination
Penicillin G	Probenecid	Increase the serum concentration	Therapy monitoring
Cephalosporins	Probenecid	increase the serum concentration	Therapy monitoring
Daptomycin	HMG-CoA reductase inhibitors (statins)	Increase skeletal muscle toxicity	Avoid combination

[a] *LMWH* low molecular weight heparins
[b] *PPI* proton pump inhibitors
[c] Antiarrhymics – propafenone, dronedarone
[d] Azole antifungal agents – fluconazole, itraconazole, ketoconazole

Adverse Events Impact

Among orthopedic surgeons, there is a common belief that side effects of prolong antibiotic treatment are mild and there is no need of treatment interruption [1, 2, 15]. In fact, none of the published studies on treatment of PJI have discussed this issue. Antibiotics commonly used in PJI treatment are very likely to cause adverse events. The incidence and severity of antibiotic adverse event is increased especially in elderly patients due to their altered pharmacokinetic and pharmacodynamics patterns, comorbidities, and the presence of polypharmacy. High dosing regimen and prolonged duration of antibiotic therapy are additional factors. Severe adverse event leads to discontinuation of treatment with selected antibiotic and transition to, in most cases, suboptimal antibiotics. Additionally interruption of treatment or noncompliance with treatment regimen is highly present in case of hard-to-bear adverse events among outpatients on prolonged antibiotic treatment. All these facts have strong negative impact on the cure rate of infected total joint arthroplasty.

These adverse events are in most cases preventable or at least ameliorable if the strict and continuous therapy monitoring is implemented during hospital stay and after discharge [6, 40].

Hypersensitivity

Among all antibiotics used in the treatment of infected TJA, beta-lactams have the greatest potential to induce hypersensitivity reactions. Immunoglobulin E (IgE)-mediated hypersensitivity reactions to penicillins occur in between 1 and 10 % of exposed patients, but true anaphylactic reactions occur in less than 0.05 % of treated patients. There is an association with increased incidence when beta-blockers are used concomitantly with penicillins. Delayed hypersensitivity reactions include drug fever, erythema nodosum, and a serum-sickness-like syndrome, hypersensitivity rashes are particularly common with semisynthetic penicillins such as ampicillin, cotrimoxazol, and clindamycin. Cephalosporins, fluoroquinolones, and vancomycin are implicated as well, but to a lesser degree [39]. The use of minocycline is associated with serum-sickness-like reactions [41]. Daptomycin is associated with rare but life-threatening eosinophilic pneumonia in cases of treatment that last >2 weeks [42]. Predicting hypersensitivity is difficult. Skin testing is only helpful in predicting reactions caused by IgE antibodies. Most nonpruritic maculopapular rashes are not predictable by skin testing. Very useful in detecting the sensitization in progress is the monitoring the eosinophil count during the antibiotic therapy, especially with penicillins, vancomycin, and daptomycin. Although significant allergic disease can occur in the absence of eosinophilia, allergic disorder remains the most common cause of significant increase of eosinophil count [43].

Note

- Most allergic reactions occur within hours to 2 weeks after taking the medication. However, rashes may develop up to 6 weeks after starting certain types of medications.

- Fever, nausea, vomiting, diarrhea, abdominal pain or cramps are uncommon symptoms of a drug allergy, often unrecognizable as such.
- Eosinophil count especially during parenteral antibiotic therapy should be monitored.

Nephrotoxicity

In PJI antibiotic treatment, nephrotoxicity is relatively frequent because it is mostly dose related. Age depending changes in renal function and nephrotoxic concomitant drugs are additional factors. It must be emphasized that nephrotoxicity means toxic effect of the drug on kidneys and should not be confused with dose adjustment needed in antibiotics with predominately renal excretion because of decreased renal function. Aminoglycosides, sulfonamides (cotrimoxazole), and minocyclin may affect renal function by directly effecting tubules, while rifampicin and vancomycin are associated with acute interstitial nephritis.

Note

- Nephrotoxicity should not be confused with the fact that some medications have a predominantly renal excretion and need their dose adjusted for the decreased renal function.

Gastrointestinal Toxicity

Nausea, vomiting, and increased bowel peristalsis, sometimes amounting to diarrhea, are common, but are generally of minor inconvenience during the majority of oral antibiotic treatment regimens. Oral treatment for PJI is mostly based on rifampicin, ciprofloxacin, minocyclin, clindamycin, fusidic acid, cotrimoxazole, and amoxicillin, depending on the causing microorganism. Gastrointestinal side effects in this cases are very common and hard-to-bear because large doses are applied for a long time mainly in elderly patients with polypharmacy as a rule. Rifampicin, fusidic acid, clindamycin, and minocycline are associated with high incidence of epigastric distress, flatulence, heartburn, nausea, and vomiting. The author recommends to introduce proton pump inhibitors (PPI) until the end of the antibiotic treatment. Pantoprazole should be the therapy of choice because of the smallest impact on CYP-mediated metabolism of concomitant antibiotics. Nausea and vomiting, if present, occur mostly in 3–5 days after introduction of oral antibiotic treatment and in most cases disappears after a few days. Short-term therapy with an antiemetic is reasonable in these cases, especially considering the potential patient rejection and omission of antibiotic treatment. Diarrhea occurs in 2 % of patients on ciprofloxacin and in about 5–10 % of patients taking oral ampicillin or clindamycin [23]. The most notorious complication is *Clostridium difficile*-related colitis with high mortality rate among elderly patients. To avoid the development of pseudomembranous colitis, the author recommends to interrupt the antibiotic treatment in

elderly patients as soon diarrhea occurs and to switch to another antibiotic, if possible.

Hepatotoxicity

Several antibiotics used for treatment of PJI, including clindamycin and fusidic acid, can produce minor elevation in liver enzymes. However, rifampicin, amoxicillin-clavunate, and cotrimoxazole are associated with acute cholestatic injury. Elderly patients receiving >2 weeks of treatment appear at significantly increased risk of flucloxacillin-associated jaundice. Prolonged treatment with linezolid has been associated with severe liver failure and lactic acidosis [44]. Rifampicin has the highest rate of hepatotoxic adverse events due to prolong treatment with high doses. Hepatitis and jaundice have occurred mainly in patients with underlying liver disease and in combination with other hepatotoxic agents [45]. Serum transaminases and bilirubin should be measured at baseline and every 2–4 weeks during therapy. Elevated liver function tests per se are not a contraindication to the use of rifampicin unless they indicate worsening or acute liver disease. Strict monitoring of these patients, however, is crucial. In cases when high levels persist, rifampicin should be discontinued at once.

Note

- Elevated levels often occur transiently in 10–15 % of patients, usually during first 3–5 days of treatment with rifampicin. Rifampicin should be promptly discontinued when high levels persist.

Administration Type Impact

Due to high dosing of antibiotics used in treatment of PJI, the occurrence of peripheral vein thrombophlebitis during intravenous therapy is very likely, especially with antimicrobial agents available in powder. The incidence of adverse events due to intravenous administration depends directly on reconstruction technic (filters should be routinely used to minimize particle contamination), diluent used, concentration of the reconstructed solution and flowrate. Clinical signs of peripheral vein thrombophlebitis (i.e., increased CRP level, fever) are too often underestimated and wrongly interpreted as symptoms of the current infection rather than side effects of the intravenous therapy. The highest rate of complications related to intravenous administration is present with strongly acidic drugs such as vancomycin, penicillin G, and ceftazidime.

The rate and clinical importance of these complications can be highly reduced or prevented by following precise reconstruction and administration instructions provided by pharmacy service and adapted to each case separately.

Fluid and electrolyte overload is another possible, but in clinical praxis often overlooked adverse event after administration of large parenteral doses of certain antibiotics, available as sodium or potassium salts. Ampicillin, piperacillin and ticarcillin, imipenem/cilastatin and ceftazidime contain high quantity of sodium. Large doses for prolonged time can result in sodium overloading and congestive cardiac failure, particularly in patients with impaired renal function. Thus, sodium-containing agents should be avoided in patients who are edematous or hypervolemic. Penicillin G is available as sodium or potassium salt. Alternating both types of salts when large doses are needed is advantageous in patient with impaired renal function.

How to Avoid Pitfalls?

Medicine Reconciliation

Medicine reconciliation is the process of comparing a patient's medicine orders to all of the medicines that the patient has already been taking. This reconciliation is done to avoid medication errors such as omissions, duplications, and dosing errors at every transition of care [46]. Interventions by clinical pharmacists also address and correct some of recognized weaknesses in prescribing arrangements due to drug interactions. In this way, the negative impact of drug–drug and drug–disease interactions on efficacy of antimicrobial treatment can be avoided or minimized.

Perioperative Medication Management

In the case of surgical intervention in PJI surgery-specific drugs and typical medications used for the treatment of intra- and early post-operative complications can interact with concomitant antimicrobial agents, leading to significant adverse events. On the other hand, parenteral antibiotic treatment as a rule in early postoperative period can result in high increase of surgery-related complication rate. Elderly patients with significant renal failure, presence of pulmonary embolism, significant electrolyte imbalance, excessive blood loss are the most frequently exposed to this danger. The selection of antibiotic agent and its dosage regimen should be promptly adjusted on patient current status.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is defined as a strategy by which the dosing regimen for a patient is guided by repeated measurements of plasma drug

concentrations [47]. TDM is used to avoid drug toxicity and to improve therapeutic efficacy. In PJI it is reasonable to undertake TDM during treatment with vancomycin and aminoglycosides (gentamycin), especially in elderly patients, receiving >2 weeks of treatment, significant blood loss (hemoglobin < 100 g/L) and renal impairment. It must be emphasized that the inappropriate timing of blood sampling leads to misleading results!

Drug Therapy Monitoring

Monitoring drug treatment allows for assessing the degree of therapeutic response and detecting the adverse events. Through targeted routine lab testing it is possible to detect declinations prior the adverse events occurrence. Laboratory tests include monitoring parameters for liver and kidney functions, complete blood count and all other relevant laboratory data, depending on pharmacokinetic and pharmacodynamic profile of the target drug. The frequency of these tests should be based on clinical judgment of the patient's status and the anticipated frequency of the incidence of the potential singular adverse event.

Patient Compliance

In prolonged antibiotic treatment, patient adherence to therapeutic regimen is of great importance for good clinical outcome. Patient compliance influence on treatment failure is underestimated. In published studies on the treatment of PJI, this issue is regularly missing. Duration of antibiotic treatment and hard-to-bear side effects are the main reasons for poor compliance, increased by older age, lower educational levels and lower socioeconomic status. Strategies for improving patient compliance include better patient education, clear and simple instructions, tailoring the treatment to the patient's life-style, encouragement of family support, informing patients about side-effects, monitoring of adherence and provision of feedback to the patient in case of problems.

Conclusion

Current recommendations for the treatment of PJI include prolonged antibiotic treatment with application of high doses because of biofilm resistance pattern. Rifampicin-based combination regimen is the most common due to high incidence of staphylococcal infections. Although drug-related complications in patients with PJI are common and severe, orthopedic surgeons still underestimate their impact on the treatment failure.

The majority of patients with PJI are elderly and are prone to hard-to-bear adverse drug events which can lead to treatment failure. In this population, the adverse event rate is higher than in younger adults due to clinically significant changes in renal and hepatic function, and body composition associated with aging. Polypharmacy is another important issue which must be taken into account when introducing antibiotic therapy. Unexpected drug–drug or drug–disease interaction can result in high incidence of adverse events, leading to antibiotic treatment discontinuation and significant increase in patient morbidity and mortality rate.

Another important issue is patient adherence to antibiotic treatment. Especially out-patient compliance can be very poor due to duration of therapy and high rate of adverse events.

There are therefore different approaches from clinical pharmacy service for the prevention of drug-related complications impact on treatment failure:

- Medicines reconciliation of newly introduce antibiotic agent with already taken drugs
- Perioperative medication management in surgery patients
- Monitoring of medicine therapy
- Assuring in-patient and out-patient compliance during antimicrobial therapy

In this way the majority of drug-related complications can be avoided.

Take Home Messages

- Medicines reconciliation, perioperative medication management, monitoring of medicine therapy and assuring in-patient and out-patient compliance during antimicrobial therapy are essential tools for avoiding drug-related complications during antibiotic treatment of infected TJA.
- The dosing regimen of parenteral antibiotic should be always adjusted to individual patients before its introduction.
- When a change/adjustment in concurrently medication therapy with introduction of antibiotic treatment is needed, the readjustment should be done after the discontinuation of antibiotic treatment.
- Routine out-patient clinical pharmacy services should be adopted for patient on prolong antibiotic treatment.

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