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RATIONALLY ASPECTS OF ANTIBIOTICOTHERAPY IN PATIENTS TREATED WITH DIALYSIS

ASPEKTY RACIONALITY V LÉČBĚ ANTIBIOTIKY U DIALYZOVANÝCH PACIENTŮ

(diploma thesis)

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CONTENT

1 INTRODUCTION

Rational use of drugs means that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.[1]

In general terms rational pharmacotherapy is worldwide accepted concept, relevant to European countries also. Among essential principles of rational pharmacotherapy still belongs evidence-based drug. It is crucial in transfer of knowledge from clinical research outcomes to clinical practice. Another principle is to search out and used only credible data and information. Created according guidelines and standards arise from condition of clinical practice. Major sense has health technology assessment process. This process describes procedure about attestation of efficacy, safety, and cost-effectiveness.[2]

Despite medical and technological advances, that have produced hundreds of drugs that are safe and effective against bacteria, viruses, fungi and parasites, infectious diseases are still a major cause of death, disability and social and economic problems around the world.

Tendency of work was chart range of adherence to created national guidelines. Further gain all available data about the patients from whole period of their treatment due to infection disease, which are important for description of patterns in prescribing of antibiotics.

The aim of theoretical part of research was to study the principles and recommendations for rational antibioticotherapy (both treatment and prophylaxis) together with survey of descriptions about pharmaceutical care of patients with renal replacement therapy.

The aim of practical part was evaluation of all cases of antibiotic therapy in KMUK (Clinic of Kaunas Medical University) for patients treated with dialysis in out-patients settings during two years 2005 and 2006, compare adherence to national guidelines among two years and among two out-patient settings (in dialysis and in general practice) and look for tendencies in antibiotic pre-

scriptions practices. Finally, perform the analysis of possible reasons of non-adherence for antibiotic prescriptions that considered as non-adherent.

2 LITERATURE SEARCH

2.1 Concept of Rationality

Each nation has to establish its own drug policy, within its own political and economic realities and in the light of its own problems and possibilities. The choice made reflects its social values and culture. Although the goals of national drug policy may differ according to countries, some core objectives have been defined which can be summarized as follows: to make effective, safe, low-cost drugs of quality available to meet the needs of the entire population (so called "essential drugs"); to ensure that all drugs are used rationally; and to develop the overall development strategy of country.[3]

2.1.1 Rationality in pharmacotherapy

Rational pharmacotherapy (RPT) is conception defining principles, fundamentals and the rules of selection of interventions.[4] By this question consider pharmaceutical care (differ from traditional drug treatment), because it is explicitly outcome-orientated co-operative, systematic approach to provide drug therapy directed not only at clinical outcomes, but also at activities of daily life and other dimension of health-related quality of life.[5] Goals of therapy are necessary in order to produce and document positive outcomes. For each medical condition health care provider and the patient must agree upon clear and concise goals of therapy. Establishing goals of therapy is an essential step toward ensuring a patient will maximally benefit from drug therapies.[27]

2.1.2 The process of rational therapy

Rational therapy requires a logical approach and common sense, based on efficacy, safety, suitability, and cost. Prescribing should be part of a logical deductive process, based on comprehensive and objective information. It should not be a reflex, a recipe a "cook-book, or a response to commercial pressure. A good scientific experiment follows a rather rigid methodology with a definition of the problem, a hypothesis, an experiment, an outcome and a process of verification. This process, and especially the verification step,

ensures that outcome is reliable. The same principles are applied by treating a patient. First is necessary to define carefully the patient's problem (the diagnosis). After that, the demand is to specify the therapeutic objective, and to choose a treatment of proof efficacy and safety, from different alternatives. Next proceeding is writing an accurate prescription and providing the patient with clear information and instruction. After some time the results of the treatment should be monitor, only then procedure has been successful. If the problem has been solved, the treatment can be stopped. If not, it would need to re-examine all steps.

Choosing a treatment has two important stages. It starts by considering the "first-choice" treatment, which is the result of a selection process done earlier. The second stage is to verify that the first-choice treatment is suitable for the particular patient. [6]

2.1.3 Specificity in antibiotic therapy

The simultaneous use of multiple antibiotics in a shotgun should be avoided because of the problems of drug toxicity and sensitisation, microbial superinfections, and antagonism between certain agents. Most bacterial infection can be treated satisfactorily with a single antimicrobial agent. There are a limited number of situations, however, in which simultaneous administration of chemotherapeutic agents is warranted:

1. synergism between two antimicrobials against a specific infecting agent
2. prevention of emergence of resistance to one or both drugs
3. treatment of polymicrobial infections for which one antibiotic is not sufficient
4. initial treatment of life-threatening infections before isolation of etiologic agent

Although the choice of antimicrobial drugs must be always individualized, there are useful guidelines that can be followed.[7]

2.1.4 General guidelines in antibioticotherapy

The essential feature of effective chemotherapeutic agents is ability to inhibit microorganisms at concentration tolerable by the host. The most successful

antimicrobial agents are those that target anatomic structures or biosynthetic functions unique to microorganism.

The appropriate choice of chemotherapy for an infection depends on five considerations:

1. the infecting organism and its antimicrobial susceptibilities
2. the type of infection (e.g., bacteraemia, urinary tract infection)
3. host factors (e.g., neutropenia, concurrent illness, age, **renal function**)
4. the antimicrobial agents (e.g., dosage, routes of administration, drug interaction, potential toxicities, cost)
5. public health considerations

The wide spread use of antibiotics select highly resistant organism that subsequently pose a risk for the patients and the community.[7]

2.2 Therapy

2.2.1 General principles of antibiotic selection

The selection of appropriate antibiotic therapy depends on a number of important factors. First, antibiotics are useful only for the treatment of bacterial infections, and so general confirmation of the presence of such an infection is critical. As general rule, whenever possible appropriate clinical specimen should be obtained to attempt a culture-proven diagnosis so that the most effective antibiotics can be selected for targeted therapy and for correct duration.[10]

2.2.2 Infecting organism

Prompt identification of the causative organism is essential for the selection of appropriate antimicrobial drugs. Culture identifications of the infecting organism can offer a clue to the likely antimicrobial susceptibilities. Another necessary point is determination of the in vitro susceptibility of isolated bacteria.

The efficacy of antibiotic therapy depends of delivery to the site of infection. Transport across the blood-brain barrier varies considerably among antibiotics.

2.2.3 Route of administration

Concerning the route of administration many antibiotics are absorbed sufficiently well via the oral route to provide effective blood levels in patients with normal gastrointestinal function. The enteral absorption of some antimicrobials is impeded by food and some medication. Many antibiotics cannot be given intramuscularly because of the local pain or necrosis at the injection site. Intravenous administration must be used in treatment of major and life-threatening infections such as septic shock meningitis, pneumonia, and endocarditis. In many cases, patients are clinically stable during intravenous treatment, and it is often possible to discharge them and to administer parenteral antibiotics on an outpatient's basis.

2.2.4 Concurrent illnesses

Patients with immunosuppressive illnesses are vulnerable to opportunistic pathogens. These patients may require broader antimicrobial coverage as well as intense therapy for ordinary pathogens. The same is true to a lesser extent for patients with chronic debilitating illness. Patients with **renal insufficiency** or liver disease may be unusually susceptible to direct toxicity.

Many antimicrobial agents (e.g., penicillins, cephalosporins, aminoglycosides, vancomycin, and fluoroquinolones) are excreted by the kidney. Dosage adjustment in patients who have severe renal failure and are undergoing dialysis or peritoneal dialysis is necessary.[7]

2.2.5 Prophylaxis

Antimicrobial chemoprophylaxis refers to the use of antibiotics for preventing infection either before or very shortly after introduction of pathogenic organism (for example, after the occurrence of a compound fracture but before the appearance of clinical infection). Chemoprophylaxis is most effective when a specific drug is selected for its activity against particular organism. When prophylaxis is aimed at preventing all possible organisms from initiating infection may occur it is likely to be unsuccessful, because it only selects out the most

drug-resistant organism as the cause of any infection that follows. Most uses of chemoprophylaxis fall into three general categories: prevention of infection after exposure to a specific pathogen, prevention of specific types of infection highly susceptible individuals, and prevention of postoperative complications. In many instances, prophylactic use of antimicrobial agents is widely practiced, but convincing data validating the efficacy of this approach are not available[8].

The use of antimicrobial prophylaxis in surgery involves a risk-to-benefit evaluation that varies depending on the nature of the operative procedure. To help wound infection in patients undergoing elective surgery, antibiotics should be administered within two hours before the incision made. If prophylactic antibiotics are to be effective, administration should be timed so that therapeutic levels are attained at surgery, but selection of bacteria resistant to the drugs is avoided. Antibiotics should usually be stopped 24 hours after the procedure.[9, 7]

The prevention of surgical site infection remains a focus of attention because wound infections continue to be a major source of expense, morbidity, and even death.[10]

2.3 Therapeutic area

2.3.1 Infections in the dialysis patients

In our daily life we are surrounded by a wealth of microorganisms, the majority of which are inoffensive.[10]

In dialysis patients, there is impairment of several aspects of lymphocyte and granulocyte function. Bacterial infections occur more often in these patients than in their counterparts; the increase is probably related more to the frequent violation of normal skin and mucosal barriers than to the immune system dysfunction. Also we can discover more seriousness in infections and resolve less promptly than in nonuremic patients. Another division of bacterial infection may be according access site.

Access site infections related to the access site are the source of 50-80% of bacteremias. The infection rate of permanent AV fistulas is lower than with AV grafts. Generally clinical manifestations of bacteremia are chills, fever,

redness, and tenderness. Delayed treatment of sepsis in dialysis patients is an important cause of morbidity and mortality. In a recent study (Marr et al, 1997), 40% of catheter-treated patients developed at least one episode of bacteremia over a 9 months period.

Into the second, **unrelated to the access site**, belong urinary tract infections, especially those with polycystic kidney disease. Further are respiratory tract infections, mainly pneumonia, which is an important cause of mortality in this population. We can mention intra-abdominal infections like a diverticulosis and diverculitis. The incidence of tuberculosis has been estimated to be as much as 10-fold higher among hemodialysis patients than among general population. Specifications of next infections are septicemia caused by Salmonella, Helicobacter pylori infections, and listeriosis.[11]

Pulmonary infections span a wide spectrum, ranging from self-limited processes to life-threatening infections and from acute illness to chronic inflammatory diseases. The widespread use of antimicrobial agents has led to the emergence of drug-resistant strains; thereby altering and expanding the range of pathogens are responsible for pneumonia, especially in hospitalized patients.[7] The causes of community-acquired pneumonia are Streptococcus pneumoniae and then Haemophilus influenza. The so-called atypical pneumonias are caused by Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila.[17]

Urinary tract infections are further one of the most common bacterial infectious diseases. Depending on the localization and the effectiveness of pathogenetic factors, various clinical pictures (lower urinary tract infection, pyelonephritis, asymptomatic bacteriuria) have to be differentiated. There are virulence factors of microorganisms on the one hand and defense mechanisms on the other, which influence the manifestation and the course of disease.[12] In nephrology patients are the most common acute and chronic pyelonephritis. Acute pyelonephritis also must be distinguished from chronic pyelonephritis, where the number of occurrences is higher in patients with progressive renal failure.[13]

Skin associated kind of infection in these patients is "A-V" fistula infections. Even with excellent placement technique, bacteria can enter the bloodstream directly through the catheter during dialysis. Bacteria from the skin can also move down the catheter and enter the bloodstream. Generally physicians must remove the catheter so the body can fight with the infection.

2.3.1.1 Principles of drug therapy in patients with renal disease

Patients with reduced renal function commonly require drugs therapy for various associated conditions. Most drugs are fully or partially excreted by kidney. Therefore dosage regimen often needs to be adjusted for order to provide safe yet effective treatment for patients with renal disease. In addition, certain therapeutic agents have potential nephrotoxicity and pharmacologic action that may endanger already reduced renal function. Understanding of drugs pharmacology, the therapeutic doses and speed of drug elimination in a given patients will lead to correct assessment of drug regimen.

2.3.2 Chronic renal failure

Chronic renal failure (CRF) may be defined as a condition characterized by uraemia, acidosis, osteodystrophy, neuropathy, and general debility frequently accompanied by hypertension, oedema and susceptibility to infection resulting from significant reduction in the excretory, homeostatic metabolic and endocrine functions of the kidney that occur over a period of months or years. The symptoms of CRF generally manifested when the glomerular filtration rate has fallen to about 15 ml/min.

Chronic renal disease generally progresses through four stages:

1. renal reserve reduction
2. renal insufficiency
3. CRF
4. end-stage renal failure (ESRF)

Reduction in renal reserve

The kidney usually has greater capacity to function than is required under normal conditions. This extra capacity is termed "renal reserve". In the early stages of chronic renal disease, damage to kidney eradicates this response for con-

ditions that place additional demands upon the kidney, such as pregnancy or increased dietary protein, cannot adequately be met.

Renal insufficiency

In this stage, toxins such as creatinine and urea that are normally excreted by the kidney begin to accumulate, although electrolyte levels often remain within normal limits as a result of homeostatic adaptations. Compensation will unavoidably result in imbalances elsewhere, such as acidaemia, bone disease, and changes in hormone level, for example parathyroid hormone.

Chronic renal failure

A progressive decline in renal function produces a wide range of both biochemical and hormonal abnormalities. Symptoms may still be insignificant despite severe disturbance of homeostasis.

End stage of renal failure

ESRF is characterized by uraemia and wide spectrum of gastrointestinal, dermatological and CNS symptoms. End-stage kidney disease occurs when the kidneys are no longer able to function at a level that is necessary for day to day life. It usually occurs as chronic renal failure worsens to the point where kidney function is less than 10% of normal.[14]

2.3.2.1 Incidence and causes

Accurate information on the incidence of CRF is difficult to obtain but some data are available from community – based studies and registries of patients entering renal replacement programmes. The incidence of CRF in men is at least 1,5 times greater than in women and this difference becomes more pronounced with age. The increasing incidence of CRF with age is attributable to non – immunological causes including vascular disease and undiagnosed prostatic disease in men. There are also racial differences in the incidence of Afro – Caribbean and Asian population in comparison with comparable white population. These differences might result from greater severity of hypertension in Afro – Caribbeans and diabetic nephropathy in Asian groups, but other factor, such as social deprivation may also contribute.

The reduction in renal function observed in CRF results from damage to the infrastructure of the kidney. It is thought nephrons are lost as complete units with all functions lost simultaneously. The remaining nephrons cope initially with the increase demand upon them. The patient remains well until so many nephrons are lost that the glomerular filtration rate can no longer be maintained despite activation of compensatory mechanisms. As consequence the GFR progressively declines. The patients may well remain symptom free until the GRF falls as low 15-20 ml/min.

CRF arises from a variety of causes (e.g., chronic glomerulonephritis, pyelo-nephritis, diabetes, polycystic kidney disease, and other). The difficulty in establishing a diagnosis of CRF increases in patients aged over 65, However, establishing a cause is useful in the identification and elimination of reversible factors, in planning for likely out comes and treatment needs, and for appropriate counselling when a genetic bases is established.

Chronic glomerulonephritis should not be regarded as a single disease as there are many forms, which may be either idiopathic or part of systemic disease. The precise aetiology is unknown but it is though to be mediated by deposition of immune complex in the glomerular tuft with subsequent development of an inflammatory response. Responsible antigens include certain strain of streptococci, other infection such as malaria, endogenous antigens from, for example neoplastic lesions, DNA, for example in systemic lupus erythematosus, and certain drugs, including non – steroidal anti – inflammatory agents, gold, and penicillamine.

Hypertension is both a common result and a frequent cause of CRF. It may be prevented by adequate treatment, thereby preventing a further decline in renal function.

Chronic pyelonephritis refers to chronic inflammation of the renal parenchyma with scarring of the kidney. It is generally caused by recurrent urine infection, which may be secondary to outflow obstruction or reflux nephropathy.

Metabolic diseases, where the most common is diabetes mellitus may lead to chronic glomerulonephritis.

Urinary obstruction may develop insidiously and the classical symptom of oliguria or pain may even be absent. Causes include prostate hypertrophy, renal calculi, congenital abnormalities, vesicoureteric reflux.

Interstitial nephritis is caused by inflammation of the interstitium of the kidney with secondary involvement of the tubules is often effected by toxins. Drugs such as penicillin, analgesics, and diuretics are typical toxins. Interstitial nephritis is more common in those patients aged over 65, possibly because people in this group are prescribed greater number of drugs.

The principle **congenital abnormality** encountered is adult polycystic kidney disease. This is an autosomal dominant inherited condition which results in the formation of multiple cysts in both kidneys throughout life. The kidneys become enlarged and frequently fail in middle age.

2.3.2.2 Diagnosis, investigations, and monitoring

The diagnosis may be suspected because of signs and symptoms of renal disease. More often CRF is discovered during investigation of other medical problems or following other routine screening.

Family, drug and society histories are all important in elucidating the causes of renal failure, since genetic or exposure to toxins, including prescription, over – the – counter and herbal drug, might be implicated.

The history of CRF often includes a long of period of polyuria (excessive urine production), usually with nocturia (walking at night to pass urine). The symptoms of uraemia are usually non-specific and include lethargy, breathlessness, anorexia, and nausea. When these symptoms occur they are often exacerbated by anaemia resulting from a reduction in erythropoetin production. Other anamnestical symptoms include an excruciating itch, poor sleep patterns, and lack of concentration and “restless leg” that may be particularly troublesome at night. Patients may also present with pigmented skin or hypertension.

Functional assessment of kidney may be performed by testing serum and urine. The serum creatinine level is more reliable indicator of renal function then the serum urea level though both are normally measured. Hyperkalaemia, acidosis

with a correspondingly low serum bicarbonate level, hypocalcaemia, and hyperphosphataemia may also be present.

Urine should be examined visually and microscopically, tested with dipstick, cultured and 24 hours collection made for determination of GFR.

The patient may report a change in urine colour, which might result from blood staining by whole cells or haemoglobin, drugs or metabolic breakdown products. Urine may also appear milky after connection with lymphatics, cloudy following infection, contain solid material such a stones, crystal casts, or froth excessively in proteinuria. Dipstick test enable simple, rapid estimation of a wide range of urinary parameters including pH, specific gravidity, glucose, blood and protein. Positive results should, however, be quantified by more specific methods.

Urinary creatinine excretion and the serum creatinine concentration may be used to calculate creatinine clearance, which approximates to GRF. As serum creatinine is determined partially by muscle bulk as well as renal function, correction for muscle mass using for patient's weigh, age and gender yield estimates of the GRF from the serum creatinine.

In some patients the kidney may be palpable. Large irregular kidneys are indicative of polycystic disease, whereas smooth, tender enlarged kidneys are likely to be infected or obstructed. However, in most cases of CRF, the kidneys appear wizened.

Structural assessment of the kidney may be performed using a number of imaging procedures, including: ultrasonography, intravenous autography, plain abdominal radiography, computed tomography, magnetic resonance imaging, and magnetic resonance angiography.

2.3.2.3 Clinical manifestations

Urinary symptoms

Polyuria where the patients frequently voids high volumes of urine could be seen in CRF and results from medullary damage and the osmotic effect of high plasma urea levels (>8 mmol/l). The ability to concentrate urine is also lost in CRF, which together with failure of physiological nocturnal antidiuresis,

results almost invariably in nocturia, where the patients will be wakened two or three times a night with a full bladder.

Proteinuria

A degree of proteinuria invariably occurs in CRF and can result from glomerular leaks, infection, and failure of protein reabsorption in the tubules or overflow or excess plasma proteins as seen in myeloma. Pronounced proteinuria (> 2 g of protein in 24-hour collection) usually indicates a glomerular etiology.

Fluid retention

As a GFR falls to very low levels the kidneys are unable to excrete salt and water adequately, resulting the retention of extra vascular fluid, which may be seen around the eyes on waking, the sacral region in supine patients and from the feet upwards in ambulatory patients. Volume dependent hypertension occurs in about 80% of patients with CRF and becomes more prevalent of the GRF falls.

Uremia

Many substances including urea, creatinine, and water are normally excreted by the kidney and accumulate as renal function decreases. Some of the substances responsible for the toxicity of uremia are intermediate in size between small, readily dialysed molecules and large non – dialysable proteins. These are described as “middle molecules” and include phosphate, guanidines, phenols, and organic acids. Clearly, there are a wide range of uremic toxins but it is the blood level of urea and creatinine that are often used to estimate the degree of toxin accumulation in uremia.

The symptoms of uremia are many and various and include anorexia, nausea, vomiting, constipation, foul taste, and skin discoloration that is presumed to be due to pigment deposition compounded by the pallor of anemia. The characteristic complexion is often described as “muddy”, and is frequently associated with severe pruritus without an underlying rash. In extremely severe cases crystalline urea is deposited on the skin (uremic frost).

Anemia

Anemia is an almost inevitable consequence of chronic renal failure and is generally noticeable when the GRF falls less than 30 ml/min (the serum creatinine is likely to be >300 μmol/l at this point.). The fall in hemoglobin level is a slow, insidious process accompanying the decline in renal function. A normochronic, normocytic pattern is usually seen with hemoglobin levels falling to between 6 and 8 g/dl in ESRF.

Several factors are thought to contribute to the pathogenesis of anemia in CRF, including shortened red cell survival, marrow suppression by uremic toxins and iron or folate deficiency associated with poor dietary intake or increased losses, for example from gastrointestinal bleeding. However, the principals cause result from damage of peritubular cells leading to adequate secretion of erythropoietin. This hormone, which is produced mainly, though not exclusively, in the kidney, is the main regulator of red cell proliferation and differentiation in bone marrow. Hyperparathyroidism also reduces erythropoiesis by damaging bone marrow and therefore exacerbate anemia associated with CRF.

Concerning clinical findings in CRF is the major cause of fatigue, breathlessness at rest on exertion, lethargy, and angina often seen in patients with CRF. These patients will also complain of a sensation of feeling cold, poor concentration and reduced appetite and libido. Compensatory haemodynamic changes occur in patients with anemia associated with CRF. Cardiac output is increased to improve oxygen delivery to tissue although this may result in tachycardia and palpitations. As a consequence many patients cope relatively well with profoundly low hemoglobin concentrations but benefit from corrective therapy.

Hyperparathyroidism (HPT)

HPT not only affects the skeletal system but also other organs especially in combination with hyperphosphatemia. The impact on cardiovascular mortality in the prevalent and incident dialysis population makes prevention of HPT obligatory. In chronic renal failure hypocalcemia, hyperphosphatemia stimulate synthesis and secretion of parathyroid hormone and cellular kinetics of the parathyroid gland. The percentage of dialysis patients in need of

parathyroidectomy increases continuously with duration of dialysis treatment. After 15 years of treatment 40% of all patients were parathyroidectomized according to the EDTA-report from 1991.[15,16]

Electrolyte disturbances

Since the kidney play such a crucial role in the maintenance of volume, extracellular fluid composition and acid – base balance, it is not surprising that disturbances of electrolyte levels (mainly, hyperkalemia, hyponatremia, hyperphosphataemia and hypocalcemia) are seen in CRF.

Hypertension and CRF changes

The vast majority of patients with CRF will have hypertension. Furthermore, raised blood pressure may exacerbate renal damage and precipitate or worsen CRF.

Severe renal impairment leads to sodium retention, which is turn produces circulatory volume expansion with consequent hypertension. This form of hypertension is often termed "salt-sensitive", as it may be exacerbated by salt intake, or "wet", as it results from fluid retention. Lesser degrees of renal impairment reduce kidney perfusion, which activates renin production, with subsequent angiotensin mediated vasoconstriction. Hypertension of this form can be termed "salt-resistant", as it is not generally salt sensitive, or "dry" hypertension owing to its dependence upon vasoconstriction may coexist under certain circumstances.

Treatment of blood pressure, irrespective of choice of therapy, generally improves to course of CRF. Eye damage in form of hypertensive retinopathy may be found in these patients whose blood pressure has not been adequately controlled. Appropriate and timely antihypertensive therapy can help prevent this.

Hemostasis

In uremia there is also an increased tendency to bleed. This is further exacerbated by anemia because of impaired platelet adhesion and modified interaction between platelets and blood vessels resulting from altered blood rheology.

Hyperlipidemia

Consideration should also be given to lipid profile of the patient and where appropriate, treatment with HMG CoA reductase inhibitors (statins) commenced. The clearance of statins is less affected by renal failure than lipid lowering therapies.[17]

Renal bone disease

Renal bone disease is a composite of high- and low-turnover bone disease. In uremia there is skeletal resistance to the action of circulating parathyroid hormone PTH, and often early vitamin D deficiency. Initiative symptoms are very rare, so biochemical and radiological test are required. Control of plasma phosphate (dietary compliance, phosphate binders), correction of metabolic acidosis (using of sodium bicarbonate), and judicious use of vitamin D analogues are needed. Over-enthusiasm however can induce low-turnover bone, with problems of increased fracture rate, and increased soft tissue metastatic calcification.[18]

Neurological changes

The most common neurological changes are non-specific and include inability to concentrate, memory impairment, irritability and stupor probably caused by uremic toxins. Fits owing to cerebral oedema or hypertension may occur. Most patients have evidence of peripheral neuropathy, although this is usually asymptomatic.

Psychiatric problems

These problems are much more common in CRF and dialysis patients. These range from depression, anxiety, and phobias, to full-blown psychosis. Sympathy, realism, education, and counseling are all important. Patients with severe mental disorders are especially challenging to manage on dialysis. Dialysis staff is becoming heavily stressed, when patients are rude and uncooperative to them. Lack of understanding, fear, and drug abuse, or undiagnosed physical and mental illnesses, can explain these occurrences in some cases.

Skin problems

Skin problems include excoriation, xerosis, nodular prurigo, pseudomyxedamatous scleroderma; "half-and-half" nails (gross shortening of distal phalanges).

Infection rates and immune system function

These are often abnormal in CRF. Infection is a common cause of death and morbidity. T – Cells function is defective, as is neutrophil activity against bacteria. Patients are notoriously hard to immunize.

2.3.2.4 Clinical intervention to retard progression to end-stage renal failure

Dietary manipulation has long been advocated as a means of retarding CRF. There are many trials. The largest of them, the MDRD (modification of diet in renal disease) study, followed 840 patients over 3 years and was not able to show differences in renal function decline between patients with and without dietary restriction. Re-analysis, and meta-analysis, can provide some suggestion that for severe renal impairment, severe protein restriction can retard GFR decline. First, because of the anorectic effect of uremia, many patients self – restrict their total calorie (and hence protein) intake. Second, there is real damage in further restricting food intake in patients already prescribed a great deal.

Blood pressure control is one of the most important therapeutic measures since there is a vicious cycle of events whereby hypertension causes damage to the intrarenal vasculature resulting in thickening and hyalinization of the walls of the arterioles and small vessels. Reduced renal perfusion leads to stimulation of the renin-angiotensin-aldosterone system.

Antihypertensive therapy might produce a transient reduction in GRF over the first 3 months of treatment as the blood pressure drops. However, it is possible that control of blood pressure will ultimately lead to an improvement in renal function. This can be sufficiently dramatic that suspension of renal replacement therapy can occasionally be warranted in patients with ESRF.

Recent meta-analysis for the period 1977-99 has suggested that ACE inhibitors provide unique nephroprotection.

2.3.2.5 Transition from predialysis to renal replacement therapy (RRT)

One of the prime reasons for timely nephrologic referral of a patient with declining renal function is to facilitate an orderly start of renal replacement therapy. Among the goals to be achieved in this setting, uppermost are reducing the rate of renal function decline to a minimum, reversing/preventing the complication of renal disease at this stage (e.g. renal bone disease, anemia, acidosis, left ventricular hypertrophy), evaluation of possibility to be transplanted, formation of dialysis access (e.g. ventricular fistula) in good time, and allowing the patient and careers to be educated about renal disease, its implication, and treatments.

RRT consists of dialysis or transplantation modalities. Further focus is directed toward dialysis treatment only. There is no precise creatinine value or GRF at which dialysis must be started. With careful attention to detail many patients can function well even with GRF values <10ml/min. In certain cases, fluid overload or hyperkalemia mandate a sudden start of RRT.

2.3.3 Dialysis as a RRT

2.3.3.1 Introduction

Hemodialysis (HD) has evolved from certainly primitive physical arrangement to a computerized, mechanical maneuver. This advance however is not what it seems – the principles of dialysis four decades ago were substantially similar to those in use now. Blood needs to be withdrawn from the circulation in a sterile way without clotting, to bathe one side of a semipermeable, across which counter flows from prepared dialysate and then be returned safely to the patient. Cannulae, anticoagulation, sterility, air embolism-all of these were major mattering in the early days-now solved by technologic advances. Initially all dialysis was seen as a “bridge“to renal recovery from injury, or until renal transplantation could take place.

Peritoneal dialysis (e.g. CAPD) has had s shorter history (starting 1975) as a chronic RRT. There were, as for HD, many technical problems in initial use.

Long-term technique survival is rarer for CAPD than for HD. In civilized society, patients should be encouraged to exercise choice about how they dialyse; this helps to involve the patient in his own long term-care. Many patients do not have the physical or mental attributes to permit self-dialysis; in these cases, unit-based HD is preferred.

2.3.3.2 Hemodialysis

Modern HD can take place at home, in a dialysis centre (satellite dialysis unit) or a main hospital site. Blood access is best achieved using an arteriovenous fistula; these depend on arterialization of peripheral veins in upper or lower arm due to exposure of veins to arterial pressure. This process can take 4 - 8 weeks to occur insertion. Vessel wall become thicker. Short and long-term tunneled venous catheters, single- or double-lumen, are further alternatives. Anticoagulation is achieved typically with a bolus and then an infusion of intravenous heparin. Treatment duration is typically for 4 hours, thrice-weekly with arterial blood flow of 250-300 ml/min and dialysate flow of 500 - 600 ml/min. The dialysis solution is essential a mixture of electrolytes in water with a composition approximating to extracellular fluid into which solute diffuse. The ionic concentration of the dialysis fluid can be manipulated to control rate and extend of electrolyte transfer. Calcium and bicarbonate concentration can also be increased in dialysis fluid to promote diffusion into blood as replacement therapy. By manipulating the hydrostatic pressure of the dialysate and blood circuits, extend and rate of water removal by ultrafiltration can be controlled.

Hemodynamic complications arise from the circulatory response mediated by receptors and the autonomic and sympathetic system. **Hypotension** occurs in 10-30% of dialysis treatment. The etiopathogenesis is complex and multifactorial –including neuropathy, antihypertensive medication, sepsis, increased body core temperature, hypoalbuminemia, and anemia. Increase sympathetic drive, accumulation of pressor compounds, and erythropoietin are other reasons for dialysis patients to be **hypertensive.** Long, slow dialysis, or more recently, daily dialysis, can normalize blood pressure without use of antihypertensives.

Sudden death rates are vastly increased in dialysis patients. This is especially the case for type 1 diabetics on HD. 80% of these sudden deaths are as a result of ventricular fibrillation. End-of-dialysis hypokalemia, hypocalcemia, and hypomagnesemia, and mild intradialytic hypoxemia are partly to blame, as are malignant ventricular re-entrant arrythmias resulting from coronary artery disease.

Arteriovenous fistulae are robust and by far the most reliable form of dialysis access. Stenosis at the site of arteriovenous anastomosis can occur early, and prevent maturation. Thanks to local aneurismal dilatation, increasing venous pressure, and reduce dialysis solute clearances. Angioplasty can resolve these difficulties. ACE inhibition may reduce the tendency to fistula stenosis; poor calcium-phosphate control may contribute to it. A good fistula can provide excellent dialysis for two decades. Central venous lines are a poor (but for patients necessary) substitute for a fistula. Infection and trombosis are chief complications.

2.3.3.3 Peritoneal dialysis

The peritoneal membrane is semi-permeable and therefore permits dialysis if a sterile dialysate is placed into the abdominal cavity. Transport across the peritoneal membrane is linked to vascular surface area and to intrinsic peritoneal permeability.

There are many different designs of peritoneal catheter now available. Usually one or two cuffs provoke subcutaneous fibrosis (help to stay the catheter). Peritoneal dialysis (PD) involves filling the abdominal cavity with dialysis fluid, allowing this fluid to live on for a while, and then draining it out to be replaced with a fresh dialysate. This takes place (as CAPD) typically using 2-2,5 liter volumes, four to five times daily, 7 days a week. All PD fluids contain sodium, calcium, magnesium, and chloride. Lactate is usually buffered. The osmotic agent is glucose-all PD is grossly hyperosmolar, and, at pH 5,2 hardly physiological.

Without doubt the most important complication of PD is infection in the peritoneal cavity. Infection can be virtually asymptomatic or cause severe systemic

upset. Symptoms are usually colicky abdominal pain and cloudy effluent (content white blood cells). Fever and raised CRP are typical. Empirical antibiotics are started (as either intravenous or intraperitoneal boluses, then added to the bags) and then changed as appropriate once PD fluid cultures have been analysed.

2.4 Antibiotics used in nephrology

The basic goal of antibiotic therapy is to achieve a steady state blood and tissue level that is both effective and non-toxic. To adjust maintenance therapy for renal failure, one of several approaches can be used. Dettli and co-workers[19] and Wagner[20] have suggested the following approach with requires knowledge concerning the relationship between the overall rate constant for elimination of the drug from the body as a percent per hour (K%) and the creatinine clearance (CrCl).[21] Antibiotics used in nephrology could be divided into classes are similar to classes used in other areas of medical and surgical therapy. Choice of representatives in particular group is reflected mainly by pharmacokinetic and pharmacodynamic features that are relevant to nephrological patient, especially such as possibility for:

1. decreased oral absorption
2. increased volume of distribution
3. decreased elimination
4. empirical judgement about infectious agents
5. increased potential for nephrotoxicity

2.4.1 Division of Antibiotics

Antibiotics are drugs derived wholly or partially from certain microorganisms and are used to treat bacterial or fungal infections. They are ineffective against viruses. Antibiotics either kill microorganisms or stop them from reproducing, allowing the body's natural defences to eliminate them. Each antibiotic is effective only against certain bacteria. In selecting an antibiotic to treat an infection is need to recognise to which bacterium is responsible. If there is one antibiotic that is predictably effective against all of these bacteria, further testing is not needed. For infections that may be caused by many different

types of bacteria or by bacteria whose susceptibility to antibiotics is not predictable, a laboratory will be asked to identify the infecting bacterium from samples of blood, urine, or tissue taken from the. The infecting bacterium is then tested for susceptibility to a variety of antibiotics. Antibiotics that are effective in the laboratory do not necessarily work in an infected person, however. The effectiveness of the treatment depends on how well the drug is absorbed into the bloodstream, how much of the drug reaches the sites of infection in the body, and how quickly the body eliminates the drug. In selecting which antibiotic to use should be also considers the nature and seriousness of the infection, the drug's possible side effects, the possibility of allergies or other serious reactions to the drug, and the cost of the drug. Combinations of antibiotics are sometimes needed to treat severe infections, particularly in the first days when the bacterium's sensitivity to antibiotics is not known. Combinations are also important for certain infections in which the bacterium rapidly develops resistance to a single antibiotic. Infections caused by more than one bacterium, in which each bacterium is susceptible to a different antibiotic, are also treated with a combination of antibiotics.

Division may be into bacteriostatically or bactericidally acting antibiotics. The other stand-point is subsumption of antibiotics into the groups according pharmacotherapeutical effect. Among activity mechanism belongs impair synthesis of bacterial wall from peptidoglycan, inhibition of protein synthesis, inhibition of nucleic acid synthesis or damage of the function of cytoplasmatic membrane.

2.4.1.1 Antibiotic classes

Penicillins

These are mainly bactericidal agents that impair synthesis of the bacterial cell wall. The penicillins may be classified into subgroups on the basis of their structure, β-lactamase susceptibility, and spectrum of action. Dosages of these agents vary according to the type and severity of infection. They are generally well tolerated. Hypersensitivity and GI reaction are the most common side effects, granulocytopenia, hemolytic anemia, bleeding intestinal nephritis,

hepatitis may occur. Patients allergic to one of penicillin compound are likely to be allergic to other such compound. Division of penicillins may be into 4 groups or subsequent;

1. Basic: Penicillin G, Penicillin V
2. Broader-spectrum: Ampicillin, Amoxicillin, and Ticarcillin
3. Penicillinase resistant: Oxacillin
4. Combination with penicillinase inhibitors: Amoxiclav, Sultamicillin

Cephalosporins

The cephalosporins are mainly bactericidal, rapidly and constantly expanding group of β-lactam antibiotics. They are bactericidal and inhibit bacterial cell wall like penicillins. The adverse effect of this group are mainly hypersensitivity reaction, local pain (with intramuscular use), and trombophlebitis (with intravenous use). Primarily the kidney excretes most cephalosporins; dosages must be reduced in the presents of renal failure. Cephalosporins can be divided into 4 generation groups. Agents: Cefalexin, Cefuroxime, Ceftazidime, Cefepime.

Aminoglycosides

The aminoglycosides are mainly bactericidal drugs that act by binding irreversibly to the ribosomal subunit of susceptible bacteria. They are not absorbed from the GI tract and must be administered intravenously or intramuscularly. These agents are ineffective against anaerobes and enterococci, so they are used chiefly to treat infection caused by aerobic gram-negative bacilli.

Blood level should be monitored to ensure proper dosing; peak levels may be lower than expected in patients with an expanded extracellular volume. The major toxicities include renal damage and ototoxicity (vestibular or auditory).The aminoglycosides are extremely active antibiotics that have proved to be clinically effective against many serious infections, and these agents have become inexpensive. New tendency to improve the toxic-to-the-rapy ratio of aminoglycosides include on-daily dosage schedule. To determine the future role of them, the cost-effectiveness needs to be compared directly with that of the new β-lactams and the fluoroquinolones.

Agents: Gentamicin, Tobramycin, Amikacin.

Tetracyclines

Tetracyclines are mainly bacteriostatic drugs that were originally employed because of their broad spectrum of activity against both gram-positive and gram-negative bacteria. The emergence of resistance among gram-negative bacilli, group A streptococci, and pneumococci and the frequency of superinfections have also tended to decrease indication for their use. They are useful in the treatment of pneumonia (caused by Mycoplasma pneumoniae), urogenital infection (C. trichomatis), and other chlamydial diseases. The tetracyclines are available in oral and intravenous formulation, its long half-time allows administration in one or two daily doses, and it does not accumulate in the presence of renal failure. These should be not given to children younger than 9 years or to pregnant woman, because of permanent discoloration of teeth may result. Other potential side effects include photo-toxicity, allergic reactions, and enterocolitis. Main agent: Doxycycline.

Macrolides

The macrolides are mainly bacteriostatic drugs, composed of 14, 15, or 16 carbon atom joined together in a complex, central, circular molecule that is linked to various side chains. Mainly used agents: Erythromycin, Clarithro-mycin, Azithromycin.

Erythromycin is excreted a large extent in the bile and only to minor degree in the urine. The dosage need not to be altered in presence of renal insufficiency It is active against gram-positive bacteria such as penicillin-sensitive S.pneumoniae, further Mycoplasma, Legionella, and Chlamydia species, it is an effective treatment for patient with atypical pneumonia.

Clarithromycin exhibit excellence activity against M. catarrhalis and H. influ-enza, which therefore makes it an attractive agent for the treatment of respiratory tract infection. The drug is being used for monotherapy for Helico-bacter pylori gastric infection.

Trimetoprim-sulfamethoxazole

Used of this combination (mainly bactericidal) extended the list of clinical situations in which sulfonamides appear to be of value; recurrent bacteriuria and urinary tract infection, prostatitis.

Fluoroquinolones

The fluoroquinolones are bactericidal compounds that act by inhibiting DNA gyrase with broad-spectrum activity. Most enteric gram-negative bacilli are highly susceptible; common GI pathogens, such as Salmonella, Shigella, and Campylobacter species, are very sensitive. They are rapidly absorbed from the GI tract. Penetration into body fluids and tissues is generally excellent; therapeutic concentration are readily achieve in blister fluid, bile, urine, saliva and sputum, bone, muscle and prostate. Most of them are eliminated by glomerular filtration and tubular secretion, and their dosage should be reduced in the presence of moderately severe renal failure. The fluoroquinolones appear to be very well tolerated, with mild GI and CNS side effects, or rash. They have been useful clinically in a variety of infections, including urinary tract, genital, prostate, GI, respiratory tract, soft tissue, and bone infection. Because of their extraordinary broad antimicrobial activity, their favorable pharmacokinetics, and their low toxicity, the fluoroquinolones are extremely valuable new drugs.

Nitrofurantoin

Nitrofurantoin is readily absorbed from the GI tract and rapidly excreted. Antibacterial level is achieved in the urinary tract. That is why; this drug should be employed only in the treatment of uncomplicated mild urinary tract infection or for its prevention. The spectrum of antibacterial activity includes E. coli, enterococci, and some strains of Klebsiella and Enterobacter. It should be not administered when there is significant impairment of renal function.7

2.4.2 Peculiarities of pharmacokinetic/dynamic in nephrology patients

Knowledge of pharmacokinetic principles is essential to understand dosage modification for drugs used in patients in renal failure. Dosage modification is indicated either where drugs have a low therapeutic index, or where renal

mechanisms play a major role in drug elimination. Drug renal clearance can be indexed to creatinine clearance in order to measure the degree of drug elimination impairment. In addition to effects on drug elimination, renal failure may also alter drug absorption, distribution, protein binding, and metabolism. Dialysis regimens, by eliminating drugs to a greater or lesser degree, have implications for drug therapy.[22]

Further are mentioned select antibiotics, which were used for treatment of dialysed patients in KMUK. Providing that GFR of patients with CRF less than 10 ml/min.

Penicillin

Dosage adjustment may be necessary in patients with impaired liver function when they also have renal failure. In this situation the liver may be a major excretion route. Excretion is considerably prolonged in patients with renal function impairment, there out by kidney 20-40%.

Cefuroxime

Injection: the following dosage reduction is recommended 5% to 10% of the usual dose in patients with severe renal failure. It means 750mg every 24 hours.

Oral: recommendations were provided based on a usual standard dose defined as 250 to 500 milligrams orally every 8 hours, then adjustment dosage is every 48 hours.

Ceftazidime

An adjustment is recommended 500mg every 48 hours.

Oxacillin

Dosage adjustment of oxacillin is not required in patients with renal failure.

Amoxicillin

Generally, dose reduction is not required unless severe renal impairment. Then is 250 mg or 500 mg every 24 hours. Additional doses should be administered both during and at the end of dialysis.

Amikacin, gentamicin

Adjustment may be based on serum level measurements, e.g., recommended therapeutic amikacin serum levels are: peak levels of approximately 25

micrograms/milliliter and trough levels of approximately 5 to 8 micrograms/milliliter). Adjustments may be 20% to 30% of the dose every 24 to 48 hours.

Vancomycin

Administration should be 500 mg every 48 to 96 hours. If the patient is anuric, a dose of 1000 milligrams every 7 to 10 days has been recommended. The initial dosage should not be less than 15 mg/kg. The optimal dose and interval can be determined based on serum drug concentrations.

Ampicillin

Patients should receive common dosage of ampicillin every 12 to 16 hours.

Ciprofloxacin

Intravenous or oral ciprofloxacin may be used in dosage 200 to 400 milligrams given every 18 to 24 hours.

Clarithromycin

In the presence of severe renal impairment the dose should be halved or the dosing interval doubled.

Doxycycline

Dosage adjustments are not required. The usual recommended dose will not lead to accumulation of doxycycline in the serum.

Nitrofurantoin, trimetoprim

Patients with moderate to severe renal failure, the use of these drugs should avoid.[23]

2.5 Pharmacotherapeutical problems as a reason for non rationality

The goal of pharmaceutical care is to prevent drug therapy problems before they occur and to resolve problems that already exist. It concern to promote health, prevent disease, and assure that drug therapy regiments are safe and effective. A drug therapy problem, however, is a patient problem that is either caused by or may be treated with a drug.[26] However, despite improved availability, pharmaceuticals are frequently used irrationally. The International Net-

work for the Rational Use of Drug (INRUD) has been established to help address this problem.[24]

There are no "magic bullets" for improving the quality of health care. There are, however, a wide range of interventions available that, if used appropriately, could lead to substantial improvements in clinical care derived from the best available evidence.[25]

2.5.1 General considerations

What is drug therapy problem? These are undesirable events or risks experienced by the patient that are involve or are suspected to involve drug therapy and inhibit or delay him/her problem achieving the desired goals of therapy. Drug therapy problems are identified during assessment process, so that they can be resolved through individualized changes in patient's drug therapy regimens. Recognize these troubles may be by sociological and pharmacological knowledge of the patient, disease, and drug therapy information collected during the assessment step.

How to discover pharmacotherapeutical problems? Practitioners gather history, evaluate data, and identify drug therapy problems; they must also determine the cause of each problem. The cause is important because it suggest potential therapeutic plans that may be implemented to solve the problem. A pharmaceutical care approach to practice is required to be able to identify a patient with a problem, rather than a problem with a prescription.

Drug therapy problems may be actual or potential. The distinction between the two is important, but is not always immediately apparent in practice. An actual problem is one that has already occurred, and thus the practitioners must try to fix it. A potential problem is one that is likely occurring. When an actual drug problem exist, then is necessary to resolve it, beside a potential problem is needful to prevent it.[26]

Short-course antibiotic therapy should be reason for out-patients, where compliance has always been problem. Investigators attempt to formalize the shortest possible course, to increase patient's adherence and reduce costs.[10]

2.5.2 Special considerations in pharmaceutical care

To identify, resolve, and prevent drug therapy problems, the practitioner must understand how patients with drug therapy present in the clinical settings.

Categories of drug therapy problems and common causes: unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low or too high, adverse drug reaction, non-compliance.

Once categorized, it is then necessary to identify the cause for each drug therapy problem. When knowing the cause of problem, it leads to the best solution for the patient. The problems have to be prioritized to determine which should be addressed first and where should be targeted the biggest pharmaceutical care and appropriate interventions.[27]

2.5.2.1 Specificities in nephrology department

Type of patients and infections treated in nephrology department is quite mosaic and reflects broad variety of infections with all possible pharmacokinetic and pharmacodynamic factors influencing antibioticotherapy. Problems relevant to nephrological department is not known and should be investigated in detail.

To find specific problems in nephrology department there are few steps have to be discovered and resolved. Firstly is necessary to describe the situation in chosen area, what we proceed with data collection of dialysed patients. Next step is evaluation of these inputs.

We tried to evaluate adherence to peer reviewed recommendations, so that we divided the drug using into three segments according the approaching the rational use of drugs. In more details, these segments are described further. Final goal of this work was to help physicians from nephrology department to re-evaluate their prescribing behaviours and improve these behaviours in future, if possible.

As one of drug problems we found the deviation from choice of the suitable medications for relevant infection disease. These were indications not fitting under the first or alternative choice for specific illnesses. Often, it is used

antibiotic with a wide broad spectrum of effectiveness, which leads to spread resistance.

Next distinguished problem is highly modest of use the microbial test for discover micro-organisms, which are responsible for emerging the infection. Even we disclose some situation, when the culture test was proceed and identify the sensitivity and resistance, but finally was prescribed the antimicrobial agent with resistance for respective bacteria regimen.

After presentation and discussion with physicians about possible problems, suitable steps and intervention for improvement the pharmaceutical care can be provided.

3 PRACTICAL PART

3.1 Background and Objectives

Theoretical evaluation of situation and possibilities of antibioticotherapy in dialysis population revealed lack of knowledge of pharmaceutical care in this area.

Since, one of first steps in pharmaceutical care is the evaluation of the situation to be intervened, we realised the need for filling this gap. We have chosen one nephrological department that is representative for tertiary care in EU country. Since this was first type of study in this setting, retrospective study design was chosen.

Research protocol was initiated to gather this information. Ethical committee approval before start of study was obtained.

Aim

The primary aim of this study was to investigate non-adherences to national guidelines on rational antibioticotherapy as a one of main aspects in rationality of antibioticotherapy in patients treated with dialysis.

Tasks

To reach this aim we had to solve several related tasks:

1. Describe ABT cases in patients treated with dialysis treatment modality during two consecutive years;
2. Investigate level of non-adherence of the prescribed antimicrobial drugs to nationally available guidelines;
3. Investigate reasons for non-adherence as this is perceived by prescribing physicians;
4. Compare the number of antibiotic prescriptions and incidents of non-adherences observed in case of dialysis population with out-patients treated in general practice during one year.

3.2 Setting and study design

Our main set included dialysed patients in Clinics of Kaunas Medical University (KMUK) in Lithuania. Group I contains patients who are registered in

nephrology department in KMUK with diagnosis renal replacement therapy in 2006, at that time of investigation (September 2006–January 2007) and were treated during period of 2005 and 2006, Group II contained historical data gathered for year 2005 in one Family practice clinic that stayed in KMUK in January 2006.

These patients needed special attitude concerning their treatment. We checked the choices of particularly agents and evaluated, if it was suitable for the rational use of drug policy, as this is recommended by national guidelines on rational antibioticotherapy.

After evaluating antibioticotherapy cases and considering certain cases of non-adherence, we studied which factors are the most influential in guiding non-adherent antimicrobial choices. Main focus was to investigate the level of non-adherence as the one of the main aspects of rationality in antibioticotherapy.

In general we evaluated the data from two different settings. First group (I gr.) included dialysed patients (DP) and second group (II gr.) consisted from patients, who were from general practice (GP).

The main quest was to discover how physicians respect and follow the national guidelines. Our effort was aimed at evaluation of cases of non-adherence to note for guidelines on rational prescribing of antibiotics (Maciulaitis et al., 2004)[28]. Effort was to gain the areas for future pharmaceutical care inter-ventions.

Towards comparison we distribute our cohort according years namely 2005 and 2006. Assembled information concerned several units of therapy: treatment and prophylaxis (medical or surgical).

- ***Treatment*** - that means kind of chosen antibiotic with dose, dosage, duration of treatment, and way of administration of the drugs. **Term therapy case** correspond a fact, that for one indication of infection disease, patient was treated with individual kind of antibiotic. There are some cases, when was necessary to use combined antibiotic therapy, and then each case is described separately. Non-adherence was assessed as per relevance for indication, efficacy, and safety.

- ***Indication*** for treatment: shows, if culture of sensitivity of infective organism was made or patient was treated empirically.
- ***Efficacy***: deals with objective data (renal clearance, CRP, neutrophils, WBC etc.)-if available.
- ***Safety***: mentions subjective data during or after treatment (if available), monitoring of drugs, which has like a side effect damage of kidney.

Prophylaxis - that means kind of chosen antibiotic with dose, dosage, duration of prophylaxis, and way of administration of the drugs.

Our interpretation of aspects of rational prescriptions of antibiotics arises from national Lithuanian guideline[28]. Primarily we obtained all of approachable data from a well-arranged table. For majority of ABT cases there is available information regarding etiology of infection, type of prescribed antibiotics, dose, dosage, duration, other information concerning specific details like a CRB, WBC, leucocytes, cultural test, etc. According to the guideline we assigned to every cases appropriate predicted drug suitable for particular infection. Diagnosis was carried out either empirically or on the based of microbiological examination. With a cooperation of doctor's team we evaluated three possibilities namely an adherence, reasonable, and non-adherence.

Term **adherence** involves rational advancement according appropriate guide-lines and rules.

Term **reasonable** in this document means that some details differ from guideline, especially in dialysed patients with concomitant diseases the doctor have to assess circumstances concerning separately patient eventually case. Reasonable cases could be further developed for optimization of guideline.

Term **non-adherence** included every items, where evaluation of case considerably deviate from accurate practice. For example when the doctor has sufficient amount of information about etiological agent and sensitivity and resistance tests and decide for that kind of antibiotic, which the test place among the resistant. Use unnecessarily wide spectrum of antibiotics for not significant disease, treatment with such a kind of antibiotic, which for dialysed patients is better to obviate.

First of all we confront the outcomes between year 2005 and 2006 in term of rational advancement. Followed information convey of quantification and comparison in our set. Our results arise from entire accessible information evaluated one by one patient.

We compared the data obtained in year 2005 with data from 2006 for DP and for the same year 2005 for GP population.

Data for patients in I group were collected from the medical charts from Department of nephrology. All acquired information was recorded into the paper form (see Appendix 1). Data were gained with compliant cooperation of pharmaceutical students from fourth class and doctors from nephrology department. Comparative set of patients from II group were presented in study of Petrikaité at al., 2006 article[32] and were retrospectively collected from Department of Family practice, Kaunas University of Medicine. This study records regarding the prescription of antibiotics during period 1st of January to 31st of December 2005. The main goal was to evaluate the use of antibiotics in daily family doctor's practice and non-adherence to guidelines on rational antibiotic therapy.

The outcome variables were:

1. The based information about patient (11 items)
2. Pharmacotherapy (kind of antibiotic, the dosage with duration of antibiotic treatment, distinguish oral and intravenous administration, aim of treatment, indication for treatment
3. Infection disease (description with its markers)
4. Evaluation (reason why antibiotics are prescribed not rationally)
5. Table (survey of treatment)

As a design, we used retrospective analysis and comparison of all available antibioticotherapy cases in DP during years 2005 and 2006. Comparative data were collected with GP for year 2005.

Statistical analysis Data were processed with SPSS 16,0 using descriptive and comparative statistics for nonparametric values (Mann-Whitney test).

Proband requirements

Into the study were included patients, who attended the dialysis unit (start at least from year 2005) and were treated in nephrology department.

For simplification further we mentioned them like a dialysed patients DP and about their treatment with antibiotics like an antibioticotherapy of dialysed patient.[29]

3.3 Main outcome measures

Demographic data of patients received antibiotics prescriptions.[30] We accomplished quantification of non-adherence to national guideline and comparison results between years 2005 and 2006 and outcomes from two different therapeutic settings (DP and GP) during year 2005. Perceived reasons of non-adherence to guideline is a necessity for definition of major area for improvement outcomes in pharmaceutical care in this Clinic.

3.4 Results

3.4.1 Description set

Our set of the **group I** attended dialysis unit three times per a week according individual schedule. Doctors in this department hold an appointment as general practitioner also (approximately in 99% of cases), it means these physicians are responsible for drug prescribing and all implications arise from that fact.

Overall, we gained information from 113 DP patients. Twelve physicians provide health care for these patients. Number of treated patients (DP who received antimicrobial agent prescription) were 40 (year 2005) and 49 (year 2006). In total, there were 197 cases of therapy; from that 88 cases in year 2005 and 109 cases in year 2006. Total number of treated patients was 72; patients, who were not treated during 2005 and 2006 is 41. It means that some of these patients were sick in both years 2005 and year 2006.

Group II contains 1285 patients; number of therapy cases 71, and number of treated patients was 42.

For the simplification reason we describe in more detail further just group I (group of main importance) and the group II we leave for final comparison of

non-adherence to guidelines on rational antibiotic therapy; it is introduced and describe subsequently.

Description data about the set are shown in table 1.

Patients group		Screened patients	ABT patients	All cases of ABT	Patients without ABT
I group	2005	113	40	88	
	%	100	35,4		
	2006	113	49	109	
	%	100	43,4		
	2005&2006	113	72	197	41
	%	100	63,7		36,3
II group	2005	1285	42	71	
	%	100	3,3		

Table 1: Settings of patients from both comparing groups-general informations in patient's numbers (and %).

In summary, it seems that I group patients had higher prevalence of morbidity (35,5 and 43,3% annually) than II group patients (3,3% annually). Majority of patients (63,7%) were treated with antibiotics during 2 years.

3.4.2 Baseline characteristics

As a baseline data we observed besides demographic characteristics (age and gender) also additional considerable items - weight, concomitant diseases (the most frequent type), and number of antibiotic treatment items per patient. Results of frequency analysis concerning with answers for previous questions are draw up in tables 2 to 5 and Graph 1.

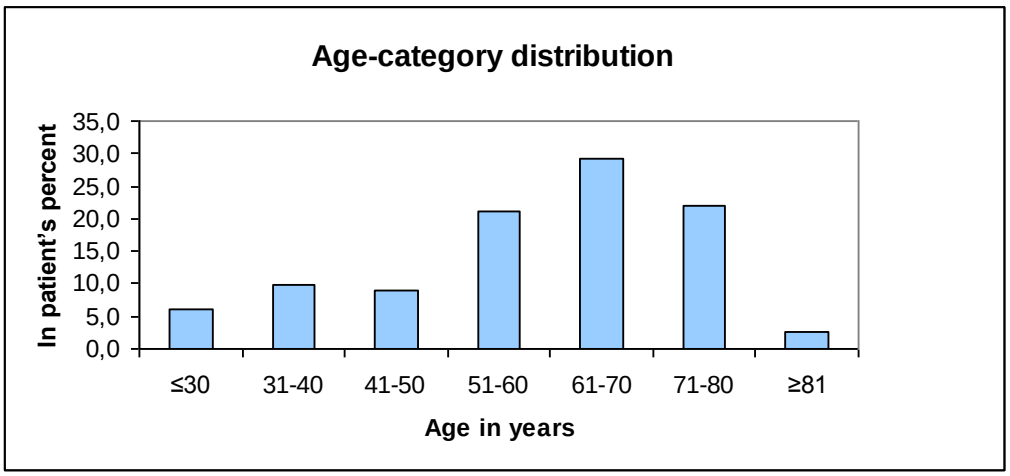
In our set of 113 patients there were 57,5% male and 42,5% female, their average age is 58,9 year. The prevalence in male cases are higher may be due to the risk factors shares by cardiovascular disease and prostatic difficulties.[31] And number of ABT items per patient was 1,3 involve both two years.

No of patients (n=100%)	Male (%)	Female (%)	Mean age (±SD)	Item of ABT/P
113	57.5	42.5	58.9(15,58)	1.3

Table 2: Baseline data about dialysed patients for both years 2005 and 2006 (in patient's numbers and %).

Patient's age (years)	Representation of patients (%)
≤30	6.2
31-40	9.7
41-50	8.8
51-60	21.2
61-70	29.2
71-80	22.1
≥81	2.7

Table 3: Age-category distribution of DP (in patient's %).



Graph 1: Age-category distribution of DP set (in patient's %).

In summary, gender distribution is approximately equal; the average data about age structure in monitored file is evident from the table 2. The most patients are in age 51-60 (21,2%), 61-70 (29,2%) and 71-80 (22,1%) years. Just 6,2% of our sample composes patients till 30 years. The ages in this group varied from 20 to 84 years old.

Regarding to concomitant diseases, all DP suffer with several relevance from hypertension and anemia, what is result from damage of kidney. The nocsequent concomitant diseases are from the highest representation hyperparathyroidism (HPTD)-15,9% follows with diabetes mellitus I, II (D I, II) and cardiomyopathia (CMP) both with 15,0%, chronic glomerulonephritis (GNCH) 12,4%, chronic pyelonephritis (PCH) 8,0%, and hyperplasia prostate 12,4% (in this case we ratiocinate 100%=65 males). The most patients of the study 38,9% are without consequential concomitant diseases.

Concomitant disease	Total (113=100%)	Males (65=100%)
HPTD	15.9	
D I, II	15.0	
CMP	15.0	
GNCH	12.4	
PCH	8.0	
HP		12.3
Without conc. disease	38.9	

Table 4: Survey of concomitant disease (in patient's%).

In summary, table 5 draw up above mentioned characteristics of our patient's set and offer general survey about monitored group. Mean age of dialysed patients is 58,9 years. Difference between genders is not prominent. Mostly of patients beside hypertension and anemia are without concomitant diseases.

Characteristic	Result
Number of patients	113
Mean age(±SD)	58,9 (±15,58)
Gender	57,5% male 42,5% female
Item of ABT per patient	1,3
Average weight	75,1
Age distribution:	
≤30	6,2%
31-40	9,7%
41-50	8,8%
51-60	21,2%
61-70	29,2%
71-80	22,1%
≥81	2,7%
The most frequent concomitant diseases:	
HPTD	15,9%
D I, II	15,0%
CMP	15,0%
GNCH	12,4%
PCH	8,0%
Without conc. diseases	38,9%

Table 5: Summary of results from the based characteristic of patient's set (in patient's %).

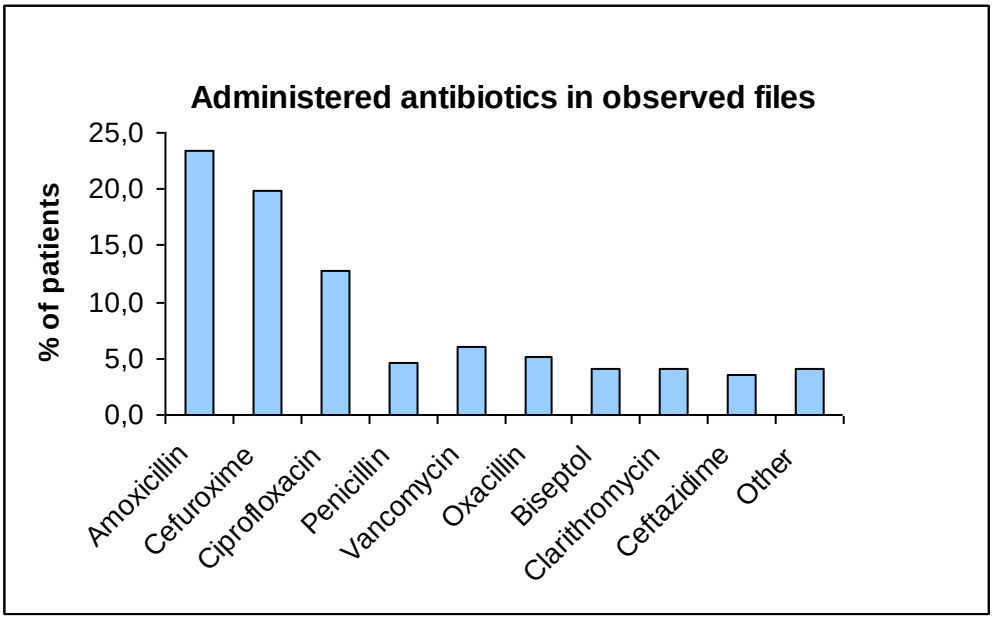
3.4.3 Pharmacotherapy and prophylaxis

In our survey extensive part deals with ABT. In our set of whole 113 patients we observed patients who are covered up therapy with antibiotics. Observed patients received the most of all amoxicillin 14,7% in year 2005, respectively 27,5% in year 2006, follows by cefuroxime 15,6% (2005), 20,2% (2006). Other prescribed antibiotics are summarized in followed table 6. Pharmaceuticals (showed in table 6 and graph 2) were used more like a multiplied medication.

Kind of antibiotic	2005 (88=100%)	2006 (109=100%)	2005&2006 (197=100%)
Amoxicillin	14.7	27.5	23,4
Cefuroxime	15.6	20.2	19,8
Ciprofloxacin	11.9	11.0	12,7
Penicillin	7.3	0.9	4,6
Vancomycin	1.8	9.2	6.1
Oxacillin	3.7	5.5	5.1
Biseptol	5.5	1.8	4.1
Clarithromycin	3.7	3.7	4.1
Ceftazidime	0.9	5.5	3.6
Cefazolin	3,7	3,7	4,1
Gentamicin	2,8	0,9	2,0
Amikacin	2,8	0,0	1,5
Ampicillin	0,9	1,8	1,5
Doxycycline	0,9	2,8	2,0
Trimetoprim	0,0	1,8	1,0
Other*	18.3	14.7	18.3

Table 6: Administered antibiotics in observed files (in antibiotics %).

*Others: Ampicillin/sulbactam,, Ceftriaxon,, Ofloxacini, Piperacillin/tazobactam



Graph 2: Selection of administered antibiotics in observed files during both years 2005 and 2006 (in patient's %).

From data fields we find that the duration of the patient's treatment take the most of all 6-10 days. Further are patients, who are treated 5 or less days. This interval is convenient for patient, who not well cooperate with a doctor and is suitable for their indication of infection. Also there is quite large number of cases, where we can't obtained this information namely proximately a third of our cohort. Summary is expressed in table 7.

ABT duration (days)	2005 (88=100%)	2006(109=100%)	2005&2006 (297=100%)
≤5	17,0	16,5	16,8
6-10	22,7	33,0	28,4
11-15	10,2	9,2	9,6
16-20	3,4	3,7	3,6
≥21	1,1	4,6	3,0
Invaluable	45,5	33,0	38,6

Table: 7: Therapy duration (in patient's %).

Main part of administered drugs was given by intravenous way, but there is a weak amount of information to disclose in percentage share. Also in many cases the intravenous way of drug delivery was switch into the oral way, when relevance of infection has diminished.

In summary, from (frequency analysis) results of pharmacotherapy and prophylaxis emerged consequent actualities:

23,4% of patients were treated with **Amoxicillin, 19,8% -** with **cefuroxime**, and **12,7%** – with **ciprofloxacin**

Most often (in 28,4% of patients) duration of treatment takes 6-10 days

3.4.4 Indication of infection diseases

Spectrum of infection diseases in our files of patients is relatively extensive and is displayed in table 8 and in graph 3.

Kind of infection	2005 (88=100%)	2006 (109=100%)	2005&2006 (197=100%)
RTI	35,2	37,6	36,5
UTI	23,9	26,6	25,4
Dermatogenic (include catheter inf.)	17,0	22,9	20,3
GIT	8,0	7,3	7,6
ORL	5,7	2,8	4,1
Infection after kidney transplantation	4,5	0,0	2,0
Other	5,7	2,8	4,1

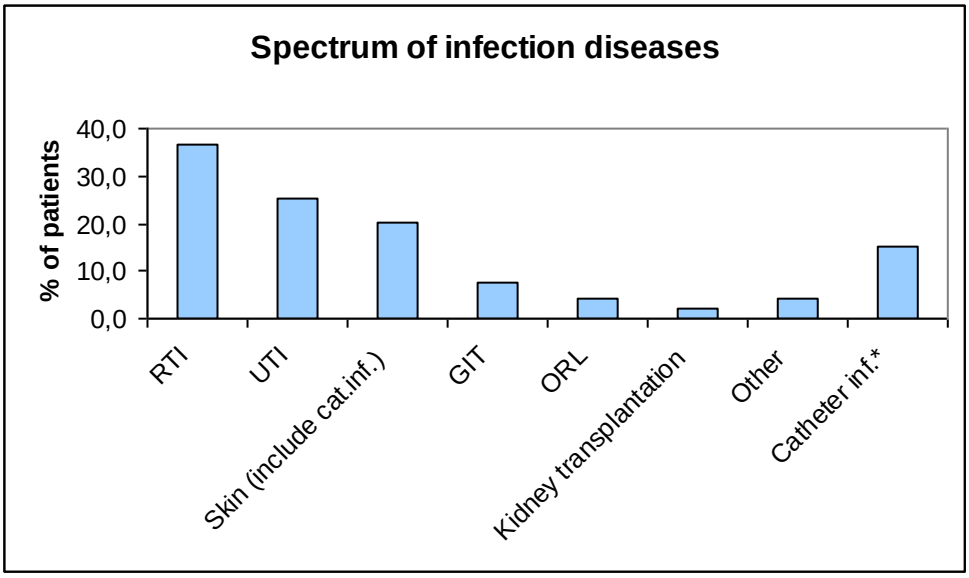
Table: 8: Distribution of infection diseases in patients set (in patient's %).

In summary, despite of that fact it is evident that some of them appear more frequently. These are respiratory tract infections (RTI), especially

pneumonia that represent more then third of all cases, followed by urinary tract infections (UTI), which gain approximately quarter of infections, dermatogenic infection with 20,3% (here is included also infections related with inserted catheter), infections covering gastrointestinal tract (GIT) takes 7,6 %, otorhinolaryngology (ORL) infections have 4,1%, infections after kidney transplantation takes 2,0%, and the other rare occur belongs 4,1% from spectrum of infections. Formerly mentioned illnesses often merge into the chronic form. Because of serious variation of infections some patients must be hospitalized during treatment. There are not significant differences between year 2005 and 2006.

	Pneumonia	UTI
2005(88=100%)	26,1	23,9
2006(109=100%)	28,4	26,6
2005&2006 (197=100%)	27,4	25,4

Table: 9: Representation pneumonia and UTI like the most frequent illness in spectrum of infection diseases (in patient's %).



Graph 3: Distribution of infection diseases of all cases in both years 2005 and 2006 (in patient's %).

As mentioned above, pneumonia itself like an infection disease covers 27,4% of all therapy cases and get into the most frequent disease of our set. The biggest representation of antibiotics, which are used to treat pneumonia, was cefuroxime with 37,0% and amoxicillin with 31,5% of cases. Nevertheless drug of the first choice is penicillin, which was used only in 16,7% cases of treatment.

Concerning UTI, this illnesses were treated mostly with ciprofloxacin, namely in case of 30% of UTI, followed by cefuroxime with 20%. These do not belong to the drug of the first choice (possibly as alternatives). The agent of first choice should be trimethoprim, which in this situation was utilized just in 4% of cases. Another significant fact was prescription of trimethoprim with sulfamethoxazol (Biseptol), in 14% of cases, while this agent is not recommended to patients with RRT. Summary outlook is in table 10.

Pneumonia		
	Total (54=100%) No	%
Cefuroxime	20	37,0
Amoxicillin	17	31,5
Penicillin	9	16,7
UTI		
	Total (50=100%) No	%
Ciprofloxacin	15	30,0
Cefuroxime	10	20,0
Biseptol	7	14,0
Trimetoprim	2	4,0

Table 10: Apply relevant kind of antibiotics for two the most frequent illness, usage of the most prescribed antibiotics for both years 2005 and 2006 (in antibiotic's numbers and %).

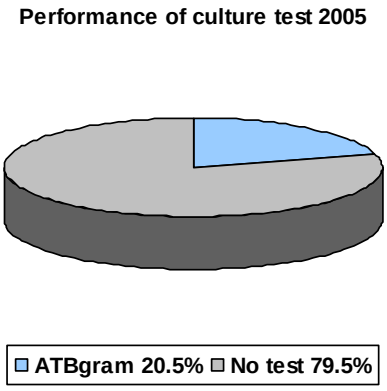
Summary of the most frequent prescription of antibiotics for two the most spread infections.

37,0% of patient with **pneumonia** were treated with **cefuroxime**
31,5% of patient with **pneumonia** were treated with **amoxicillin**
Just **16,7 %** of patient with **pneumonia** were treated with **penicillin**

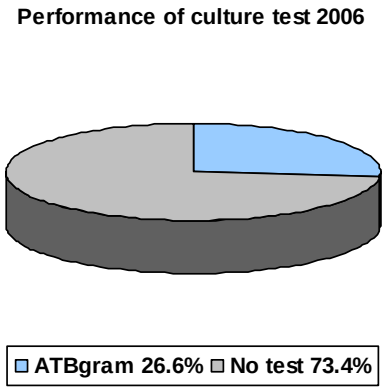
30% of patient with **UTI** were treated with c**iprofloxacin**
20% of patient with **UTI** were treated with **cefuroxime**
Just **4%** patient with **UTI** were treated with **trimetoprim**

3.4.5 Indication of treatment

According to good pharmaceutical care, before the initiation of patient's treatment should be carried out the bacteriologic test and ascertainment sensitivity and resistance for appropriate antibiotics. However most of treatment in this department is provided empirically. Bacteriological tests were performed in less then third of cases. We can see appreciable improvement in year 2006 with contrast to previous year 2005. These information displays graph 4 and 5.



Graph 4: Performance of cultural test in year 2005 (in patient's %).



Graph 5: Performance of cultural test in year 2006 (in patient's %).

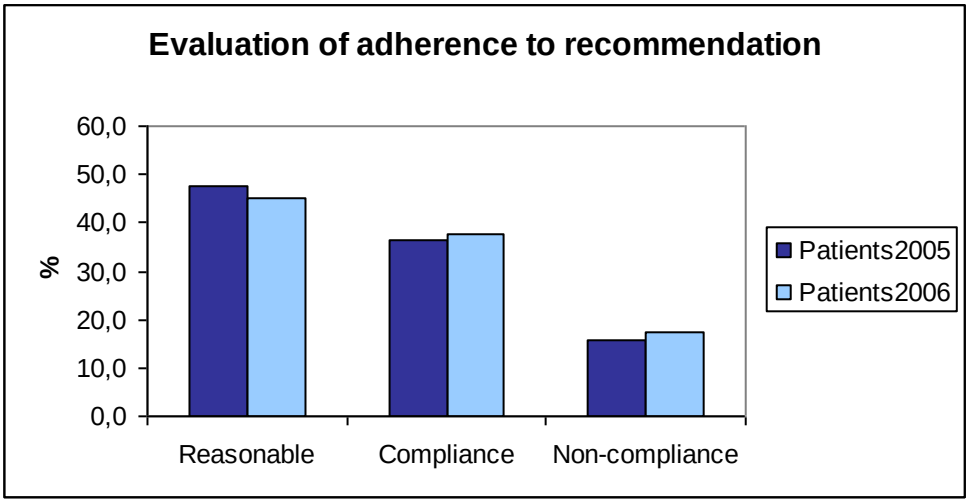
3.4.6 Rationality of ABT in DP set between year 2005 and 2006

From all cases of ABT there were 88 patients in 2005 and 109 in 2006 from that non-adherence was considered in 14 cases for year 2005 and 19 in 2006. This is statistically nonsignificant (p=0,3, Mann Whitney test). More

detailed informations are described in followed table 11 and graphs 6 and 7.

	2005 (88=100%)	2006 (109=100%)	2005&2006(197=100%)
Reasonable	47,7	45,0	46,2
Adherence	36,4	37,6	37,1
Non-adherence	15,9	17,4	16,8

Table 11: Evaluation of rationality aspects in prescription of antibiotics (in patient's %).

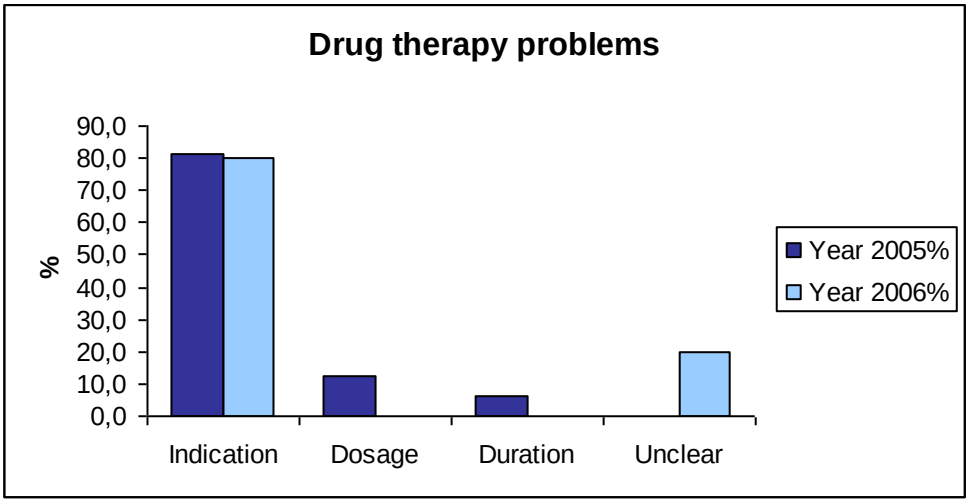


Graph 6: Evaluation of adherence to national recommendation in years 2005 and 2006 (in patient's %).

The situation on this department we can designate like a favourable from the viewpoint access to rational drug use. In the year 2006 appear mild improvement, the non-adherence to guidelines decrease from 18,2% to 13,8%.

From the considered drug therapy problems the biggest part belongs to indication for choice of proper kind of antibiotics to the particular disease. It seems that usual preference is given to that one, which has greater spectrum to cover larger amount of bacteria. Another reason for apparent failure of antimicrobial therapy is when a viral illness (e.g. upper and lower respiratory tract infection) is treated with antibacterial agents. Further often problem is

dosage too high, than is sufficient. Especially for DP this presents an issue. Some cases are unclear, in our case it means, that we have not enough information to evaluate it.Graph 7 shows the stratification of these problems.



Graph 7: Structure of drug therapy problems in DP in years 2005 and 2006 (in patient's %).

In summary, main problems raise in choice of indications. Same pattern is relevant for both years in DP population.

3.4.7 Comparison of two different patients settings in rational drug use according recommendations

Additional comparison from two different patient settings is provided. Here comparison of group I of DP and group II of GP patients from year 2005 is provided.

3.4.7.1 Description of group II file

Essential general and analysis data about II group of patients are presented in comparative manner in tables 12-15 and graph 8 that follow.

Patients group	Screened patients	ABT patients	ABT patients %	All cases of ABT	Mean age	SD
I. group	113	40	35,4	88	58,8	±18,76
II group	1285	42	3,3	71	45,2	±18,91

Table 12: Patients settings from both comparing groups-general information (in patient's numbers and %).

From patients data presented we can see marked differences. While in GP set were experienced in infection disease 3,3% of patients, in group of DP it was even 35,4%.

Table 13 presents further data regarding prescribed antibiotics according to the fact of adherence to recommendations as adherent, reasonable, or non-adherent cases. Non-adherence rate in I and II group was 14/88 (15,9%) and 39/71 (54,9%), correspondingly, what is statistically significant ($p<0,05$, Mann Whitney test).

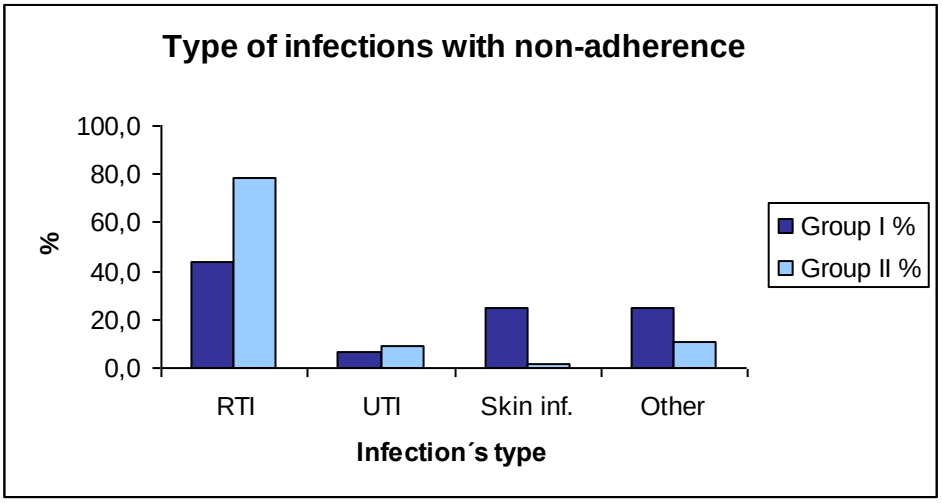
Evaluation				
Group of patients		**Adherence**	**Reasonable**	**Non-adherence**
I	Number	32	42	14
	%	36,4	47,7	**15,9**
II	Number	5	27	39
	%	7,0	38,0	**54,9**

Table 13: Comparison of two different patient settings expressed as rate to adherence of rational drug use guidelines (in patient's numbers and %).

Concerning non-adherence of separate infection diseases, our comparison shows that the extend area where was the antibiotics prescribed are different in case of respiratory tract infections (RTI), dermatogenic infections, urinary tract infection UTI, and the other. Followed table 14 and graph 8 show the rate in percentage.

Non-adherence	RTI	UTI	Dermatogenic inf.	Other
Group I	43,8	6,3	25,0	25
Group II	78,6	9,0	1,9	10,5

Table 14: Spectrum of infection with non-adherence in comparing group I and II (in patient's %).



Graph 8: Spectrum of infections with non-adherence in comparing group I and II (in patient's %).

Followed are examples of the most common cases of deviation from recommendations. Further examples provide spectrum of inappropriate behavior:

- inappropriate indication (that means the drug product is not being properly chosen for desired purpose)
- inappropriate dosage and duration of treatment

Evaluation		
Inappropriate indication		For respiratory tract infections were the most often prescribed cefuroxime, even it is neither first choice nor alternative
		UTI-the most occurs antibiotic is ciprofloxacin, which also not belongs among ones with the first choice
Inappropriate dosage		Amoxicillin in too high dosage occur like the most frequent problem in this area
Inappropriate duration		Concerning duration we lack quite a lot data, but it seems UTI is usually treated too short, when is recommended not less then 14 days

Table 15: The most frequently occurring inappropriate drug using.

3.4.7.2 Conclusion of comparison between DP and GP patients

In summary, comparative data show relatively different rate of non-adherence between both settings. Dialysed patient's population show less extend of non-adherence comparing to GP population. Larger amount of non-adherence shows potential risk for non-rational use of drugs. With majority problems, which are in cases of using cefuroxime and amoxicillin and in treatment of respiratory tract infections and UTI.

Data stress on biggest attention to be devoted during intervention in case of choice of indication. Moreover, try to utilize the formulary with rational drug use.

3.4.8 Analysis of reasons for non-adherence to guidelines

33 cases of non-adherence were analysed and recorded into the form. This is described in Attachment 1. In majority of cases, three types of reasons were noted. These were:

1. "Lack of knowledge";
2. "Fear for treatment failure";
3. "Laboratory tests results were not taken into the consideration".

Main perceived reasons for non-adherence for both years were leaded by "lack of knowledge" in 16 cases (48,5%), followed by "laboratory tests results were not taken into consideration" in 13 cases (39,4%) and "fear for treatment failure" in 4 cases (12,1%).

Reason of non-adherence	2005(14=100%)	2006(19=100%)	2005&2006 (33=100%)
1	42,9	52,6	48,5
2	14,3	10,5	12,1
3	42,9	36,8	39,4

Table 16: Reasons of non-adherence to national guidelines in years 2005 and 2006 (in patient's %).

3.5 Discussion

3.5.1 General introduction

Antibiotic treatment and prophylaxis of dialysed patients with the aim to put behind consequential complication has its own specificity. To be successful the patient has to be motivated to long-term cooperation with the physician and dialysis team. One's own treatment and also its outcomes may be perceived from health workers and patients slightly differently. Appreciation mainly negatively noticed aspects of illnesses are able to help practitioners better established relation based on respect and confidence. Therapeutic tendency are than more effective.

We accomplished investigation in nephrology department in public hospital on KMUK (2200 beds) in Lithuania, which mapped how the antibiotics are prescribed. In this area is lack information that's why we wanted to contribute with this thesis into the spectrum of pharmaceutical care. Simultaneously for purpose we confront study of Petrikaité V.[32]. Limit for this research was language barrier in the clinic, but all people who participate to create this work were extremely compliant.

The information's were collected from medical charts of patients, who attended dialysis department.

The most of dialysed patients are located in interval 51-70 years, which arise from epidemiology of renal replacement therapy, where the biggest portion of patients starts to be treated around 55 ages. With increasing age the prevalence of dialysis treatment applications raises.

Twelve nephrologists provide also care beside general practitioners. This reality results from fact that patients attend department three times a week.

Generally, we can say that outcomes of frequency analysis from separately years of dialysed patients are not markedly differential. These two groups embody high grape of homogeneity from aspect of pharmacotherapy. We can judge there is the same level of rationality in pharmaceutical care. Concerning patients from GP we found differences between them and nephrology patients. Set of GP patient show bigger extent of non-adherence to known guidelines and recommendation of appropriate ABT therapy. It arises out of the fact, that DP cohort suffer from additional concomitant disease and also larger amount of elderly patient are more susceptible to various illness.

3.5.2 The based characteristics of ABT in monitored set

Frequency analysis of demographic characteristics of monitored set- age and gender of patients-have shown, that in our pursued group are not marked differences from cohort of dialysed patients from observed study of clinical studies.

In our set makes the mean age 58,9 years from range 20 to 84 years. Prevalence of renal replacement therapy is same both males and females.

3.5.3 Pharmacotherapy and prophylaxis

For easier intelligibility of pharmacotherapy and pharmacoprophylaxis of monitored patients set was frequency analysis implement according our re-adjustment. Administered pharmaceuticals were section accordance separately case. **Term therapy case** corresponds with a fact, that for one indication of infection disease patient were treated with individual kind of antibiotic. It means that for one infection treated period with prescription for instance three consecutively antibiotic agents presents three cases. Then can be each case

consider separately and more distinctly. However, cases involving one patient were discussed and evaluating in a complex way, because it relate together.

Frequently we can found just incomplete information. The reason why is, that the information was handwritten by the physician and often without mentioned the dose, dosage, or duration of treatment.

Clearly we determined that the most of all prescribed antibiotics were amoxicillin 23,4% in a both years and cefuroxime 19,8%. These agents are with a wide broad spectrum activity.

Amoxicillin cover infections of upper and lower respiratory tract, ears infection, urogenital tract infection, and dermatogenic infections. Incident of infections in dialysed patients appear very often. Dosing has to be decreased on 250 to 500 milligrams ones time per day. Sometimes this recommendation was broken. Overall, this antimicrobial agent is support well by patients.

Cefuroxime have similar indication for infection like amoxicillin. Special utilization of this agent may perform for sequence therapy for instance pneumonia, when primarily administration is parenteral and continue with per oral delivery. With a dosing less then one gram per day is need no special disposal.

3.5.4 Indication of infection disease

Procedure for discovery type of infections disease is often accomplished on the empirical based. In spite of it we discover moderate improvement in providing of microbiological test for detect causative microorganisms. While physicians in year 2005 carried out just 20,5% culture test from all 88 therapy cases, in year 2006 already 26,6% tests from 109 therapy cases were embrace into the consideration.

Among one of the drug therapy problem we found was use of an inappropriate antimicrobial drug. Rare, but still in some cases was prescribed antimicrobial drug to which the infecting bacteria are resistant according usual laboratory tests. Such usage has been shown to be highly deleterious in terms of cure rate in patients with serious infections, but it is noteworthy that even under such adverse conditions, some cures do occur.[33]

The patients from our set were the most of all treated for lower respiratory tract infections namely 36,5% from all infection diseases and greatest representation from this portion belongs to pneumonia. In both years were experienced with pneumonia almost one third of all treated patients (precise 27,4%). For this illness physicians used mainly cefuroxime (37,0%) and amoxicillin (31,5%). Ordinarily for not serious community acquired pneumonia manages penicillin V and G. Thereof we may trace up excessive use of wide broad spectrum antibiotic agent.

On the second place appear urinary tract infections, where can be involve asymptomatic bacteriuria, symptomatic cystitis, acute pyelonephritis, emphysematous infections, papillary necrosis candidal infections, and perinephric abscess with a different degree of seriousness from mild infection up complicated illness. Here ciprofloxacin were prescribed in 30 % of UTI infections. This agent not belongs to the first choice but like an alternative drug choice.

In comparison of two different settings of DP and GP patients, noticeable difference in number of treated patients was observed in 2005 - 3,3% (GP) versus 35,4% (DP). It may origin from higher mean age and bigger amount of concomitant disease of dialysed patients. This hypothesis should be tested on enlarged set of patients.

3.5.5 Non-rationality of ABT in our monitored set

Despite of wide announcement, guidelines have had limited effect on changing physician behavior. Their adherence to guidelines may be aggravated by variety of barriers. A theoretical approach can help explain these barriers and possibly help target interventions to specific impediment.[34]

Among the relevant errors in KMUK belongs use of an agent with an inappropriate spectrum, administration of antibiotics when there is little evidence of bacterial infection, unnecessary prolonged courses, and overuse of intravenous agents. We could assume that the physicians rather choose antibiotic with a broaden spectra to be sure for effectiveness, but thereby increase resistance and unneeded overload of the patients. The results are increase side effects for the

patients, which we can obviate; spread the resistance to antibiotics for the community as a whole and deviation from adherence of guidelines concerning rationality use of drugs.[35]

The process of ensuring that guidelines are introduced into clinical practice is necessary for improvements in health care on particular departments. There is strong evidence that guidelines are often not adopted.[36] Survey have shown that compliance vary from 20% to >90%[37], depending on nature of the guideline, the specific clinical problem it is designed to address , the patients group being targeted, the mode of implementation and the definition of adherence.[38]

Non-adherence can be considered an issue of behavior, therefore, resolving this problem requires a change in behavior, sometimes on the patient's part (few of them prefers not to take or forgets to take medications). But more often the non-adherence problems require changes in the part of the health care practitioners or the system. All non-adherences have the root cause, and by determining why the advancement is not keep, can an effective solution be implemented.

These findings define a strategy for targeted intervention in nephrology setting. The records help to improve solving drug therapy problems. Important fact, that this area start to be mapped and we can arrange next steps to improve adherence to recommendation, when is still necessary to pursued the health practitioners to followed and used appropriate guidelines. Also ascertain that these practitioners, who intend to provide pharmaceutical care, understand the descriptions and identification of emerged drug therapy problem as well as their causes. As general rule, whenever possible appropriate clinical specimen should be obtained to attempt a culture-proven diagnosis so that the most effective antibiotics can be selected for targeted therapy and for correct duration.

4 CONCLUSION

In my diploma thesis I tried to illustrate the difficulties encountered when measuring the impact of interventions to promote the rational use of antibiotics. Nevertheless, I suggest a positive effect of the development and implementation of national guidelines in nephrology department, particularly when it would be reinforced by a clinical pharmacist.

From our survey, emerge subsequent results:

1. 35% (in 2005) to 45% (in 2006) of DP population annually are suffering form infectious diseases (mainly pneumonia and UTI) and are treated mainly with amoxicillin (in 23,4% of cases), cefuroxime (19,8%), and/or ciprofloxacin (12,7%) most often during 6 to 10 days of treatment.
2. Non-adherence to nationally available guidelines on rational antibioticotherapy in DP population was observed in 15,9% (in 2005) and 17,4% (in 2006) of ABT cases. Availability of bacteriological tests for indication of illness was provided in 20,5% (in 2005) and 26,6% (in 2006).
3. Main perceived reasons for non-adherence were the "lack of knowledge" in 16 cases (48,5%), followed by "laboratory tests results were not taken into consideration" in 13 cases (39,4%) and "fear for treatment failure" in 4 cases (12,1%) and for both years.
4. In comparison of two different settings of DP and GP patients there was observed noticeable difference in number of treated patients during year 2005 (3,3% in GP vs 35,4% in DP population) and incidents of non-adherences (54,9% in GP vs 15,9% in DP).

5 ABBREVIATIONS

ABT	Antibioticotherapy
A-V	Arterio-venous
CAPD	Continuous ambulatory peritoneal dialysis
CMP	Cardiomyopathia
CNS	Central nervous system
CrCl	Creatinine clearance
CRF	Chronic Renal Failure
CRP	C-reactive protein
D I, II	Diabetes mellitus type I, II
DP	Dialysed patients
ESRF	End-stage renal failure
GFR	Glomerular filtration rate
GI	Gastrointestinal tract
GNCH	Glomerulonephritis chronica
GP	General practitioner
HP	Hyperplasia prostate
HPTD	Hyper-para-thyroidism
i.v.	Intra venous
INRUD	The International Net-work for the Rational Use of Drug
K%	Constant for elimination
KMUK	Clinics of Kaunas Medical University
MDRD	Modification of diet in renal disease formula to calculate GFR
NA	Non-adherence
No (N)	number
ORL	Otorhinolaryngology
p.o.	Per os
Pg	Page
PD	Peritoneal dialysis
PCH	Chronic pyelonephritis

PTH	Parathyroid hormone
RRT	Renal Replacement Therapy
RTI	Respiratory tract infections
UTI	Urinary tract infections
vs	Versus
WBC	White blood cells
WHO	World Health Organisation

6 ATTACHEMENTS

Attachment 1: Form paper summarizing all available data about treatment of dialysed patient from medical charts (5 pages).

Attachment 1:

For each patient being treated with antimicrobial drugs

Patient's name:
Patient's identification number:

Start of collection the information's:
Name of a physician:

Gender (male / female)
Age:
Weight:
Social history: Married, smoker, special diet:

Diagnosis:
Concomitant disease(s):

History of medicament use: See Pg.4

I Antimicrobial drugs

Date when treatment start:

Name of drug	Dose	Frequency (per day)	Dosage form		Aim of treatment	
			p.o.	i.v.	Treatment	Prophylaxis
Antibiotics						
Type of infection:						

Start of antibiotic therapy <1 day 1-2 days Longer:

Duration of antimicrobial therapy: ...
Source of the antibiotic: hospital pharmacy
private other

If the therapy is prophylaxis

Surgical:
Type of operation
Was any injection during the operation? YES NO
Dose before and after operation…

Medical:
Immunosuppression
Other...

If the therapy is treatment

Do the choice of antibiotic comply to the medical record YES NO

	Acquired infections	
	Public	From hospital or <48 hour after stationary
Types of infection(s), plz show precisely in case of more than one disease.		
Sepsis		
Upper resp. tract infection		
Lower resp. tract infection		
Urinary tract infection		
Infection due to wound after operation		
Abdomen infection		
Clostridium difficile infection		
Osteomyelitis		
CNS infection		
Gynaecological infection		
A-V fistula infection		
Dermatogenic and mucous infection		
Eye infection		
Other		
Not clear at all		

II. Indication for treatment

Culture and sensitivity was made:

If yes,

From where the investigation materials were taken:

The results of laboratory tests must show to what it is sensitive:

Resistance to what:

If not,

Reason(s):

Investigation material was not taken because:

Other:

Empirical therapy

If empirical, was quick bacterioskopic diagnosis performed? YES/NO
If yes,
Investigation materials taken:
Results of the tests:

If not,
Why?
Other reason:

Localization diagnosis of the infection have been confirmed objectively
YES NO
(Show objective information)

III Risk factors for hospital infections

	YES	NO known
Urinary bladder catheter		
Central vein catheter		
Diabetis mellitus		
Artificial lung ventillation		
Previous operation <30 days		
Immunosuppression		
Transplantation		
Malignancy		
Other:		

IV Evaluation of rational antimicrobial therapy

The antimicrobial drug therapy <u>does satisfy</u> the rational drug therapy recommendation.
The antimicrobial drug therapy <u>does not satisfy</u> the rational drug therapy recommendation.

Does the doctor know about the rational drug therapy hand booklet?

Yes

No

Date:		
Drug name		**Indication for treatment:** Pg1

<table>
<tr><td></td><td colspan="3"></td><td rowspan="5"><u>Culture and sensitivity was made</u>:
Yes: type(s) of bacteria:
Material-
Sensitive-
Resistance-

No:
Reason-
<u>Empirical therapy</u>:
Bacterioscopic diagnosis.
YES/NO
Material-
Result-

<u>Localization diagnosis of the infection have been confirmed objectively</u></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td>Symp-toms of inf.</td><td colspan="3"></td></tr>
<tr><td>Type of inf.</td><td colspan="3"></td></tr>
<tr><td rowspan="3">Efficacy</td><td colspan="3"><u>Subjective data:</u>
Symptoms:</td></tr>
<tr><td>Objective data:</td><td>Before treat.</td><td>After treat.</td></tr>
<tr><td colspan="2">Renal Clearance:
Temperature:
CRP:
Neutrophils:
WBC:</td><td></td></tr>
<tr><td rowspan="2">Safety</td><td colspan="3"><u>Subjective data:</u></td><td rowspan="3">IV Evaluation of rational antimicrobial therapy: Pg2
<u>does satisfy</u>
<u>does not satisfy</u>
Does the doctor know about the rational drug therapy hand booklet?

Reason why: see Pg5
Nr:</td></tr>
<tr><td colspan="3"><u>Objective data:</u>
CrCl:
GFR:</td></tr>
<tr><td>Result analysis</td><td colspan="3">Improved:
Constant:
Death:
Worsened:</td></tr>
</table>

V. Reason why antibiotics are prescribed not rationally

	YES	NO
1.	Lack of knowledge in antibiotics.	
2.	Fear of treatment failure.	
3.	Laboratory tests results are not taken into consideration.	

7 REFERENCES

[1] WHO, Promoting rational use of drugs: core components. WHO Policy perspectives in Drugs, September 2002, Conference

[2] Sechser T., Horká R., Filip K., Rational pharmacotherapy, Remedia, s.r.o. 2006

[3] WHO, Implementation of WHO's revised drug strategy: The rational use of drug, January 1994, Information document

[4]Filip K., Sechser T., Based terminology in pharmacoeconomy and pharmacotherapy, Remedia pharmacotherapeutical periodical, 5/2006

[5] Wiffen P., Mitchell M., Snelling M., Stoner N., Oxford handbook of clinical pharmacy, Oxford university press, New York, 2007, 258

[6] WHO, Guide to Good Prescribing, Action Programme on essential Drugs, Geneva , WHO/DAP/94,11

[7] David C. Dale, M.D.: Chemotherapy of Infection, In.: David C. Dale, M.D Infection diseases. WebMD Inc., New York 2003, 17-52

[8] Osmon DR., Antimicrobial prophylaxis in adult, Mayo Clin Proc 75:98, 2000

[9] Antimicrobial prophylaxis in surgery, Med Lett Drugs Ther 41:75, 1999

[10] Cohen J., Powderly W. G., Infection Diseases, Mosby , Second edition, Spain, 2004, (3, 1705, 1749)

[11] Daugirdas J. T., Blake P. G., Ing T. S., Handbook of dialysis, Third edition, Lippincott Williams & Wilkins, Philadelphia, USA, 2001, 495-521

[12] Fünfstück R, Stein G, Naber KG, Hacker J, Marget W, Urinary tract infection, Med Klin (Munich) 2003 Jul 15;98(7):377-87

[13] Hooton T. M., Stamm W. E., Acute pyelonephritis: Symptoms; diagnosis; and treatment, Licensed to KMUK Dialize, ©2006 UpToDate®

[14] American Accreditation of Health Care Commission, End-stage kidney disease, Copyright 2005, A.D.A.M., Inc.

[15] Fassbinder W, Brunner FP, Brynger H, et al: Combined report on regular dialysis and transplantation in Europe. XX, 1989; Nephrol Dial Transplant 1991; 6 (Suppl 1): 4-65

[16] Ulrich Neyer and Helmut Hörandner, Parathyroidectomy In Renal Hyperparathyroidism, CIN 2003, 3th congress of nephrology in internet

[17] Roger Walker, Clive Edwards: Chronic renal failure. In: Marriott J., Smith S. Clinical pharmacy and therapeutics, third edition, Churchill Livingstone, Edinburgh, 2003, 247-263

[18] Pattison J., Goldsmith D., Hartley B., Fervenza F. C., Grande J. P., Chronic renal failure and dialysis. Renal drug, Manson publishing, London, 2004, 177-212

[19] Dettli L, Spring P, Ryter S: Multiple dose kinetics and drug dosage in patients with kidney disease. Acta Pharmacol (Kbh) 29

[20] Wagner JG: Relevant pharmacokinetics of antimicrobial drugs. Med Clin N Amer 58:479-492, 1974

[21] Bennett WM: Principles of drug therapy in patients with renal disease (Medical Progress). West J Med 123:372-379, Nov 1975

[22]http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6359952&dopt=Abstract

[23] Micromedex database

[24] Degnan D. R., Laing R., Quick J., Ali H. M., Ofori-Adjei D., Salako L., Santoso B., A strategy for promoting improved pharmaceutical use: the International Network for Rational Use of Drugs. Soc Sci Med. 1992 Dec;35(11):1329-41

[25] Oxman A. D., Thomson M. A., Davis D. A., Haynes B., No magic bullets: a systematic review of 102 trials of interventions to improve professional practice, Canadian Medical Association Journal 1995; 153: 1423-1431

[26] Provers J. P., Currie J. D., Hagel H. P., McDonough R. P., Sobotka J. L, A practical guide to pharmaceutical care. Second edition, APhA, Washington, DC, 2003, 15-25

[27] Cipolle Robert J., Strand Linda M., Morley Peter C., Pharmaceutical care practice. Second edition. McGraw-Hill, USA, 1998, 171-179

[28] Maciulaitis R., Miciuleviciene J., Stirbiene I. Rational use of antimicrobial preparations: recommendations for microbiological diagnostics, treatment, and propylaxis of infectious diseases. Vilnius, 2004,

[29] Vytřísalová M. :Analýza vztahu pacientů k léčbě osteoporózy I, FaF UK, Hradec Králové, 2003, Diplomová práce. 66 S

[30] Petrikaite V., Maciulaitis R., Simanaviciute L., Valeikiene J., Aukstakalniene A., Non-adherence to guideline on rational antibioticotherapy in outpatient setting, 6th ESCP Spring Conference, Vilnius, 25-27.5,2006, Poster

[31]Woerden H. C., Wilkinson J., Heaven M., Merrifield J., The effect of gender, age, and geographical location on the incidence and prevalence of renal replacement therapy in Wales, BioMed Central, Nephrology 2007, 8:1 doi:10.1186/1471-2369-8-1

[32] Petrikaité V., Mačiulaitis R., Janušonis T., Aukštakalnienė A., Assessment of antibiotic use and comparison with recommendation for their rational use, Medicina, Kaunas 2006, 42(12), 999-1005

[33] Speight Trevor S., Holford H. G., Avery's Drug Treatment, A guide to the properties, choice, therapeutic use and economic value of drugs, Adis International, 4th Edition, New Zealand 1997, 1488-1493

[34] Cabana M. D., Rand C. S., Why don't physicians follow clinical practice guidelines?, JAMA, October 20, 1999-Vol 282,No 15, 1458-1463

[35].Weller T. M. A., Jamieson C. E., The expanding role of the antibiotic pharmacist, Journal of Antimicrobial Chemotherapy (2004) 54, 295–298

[36] Woolf S.H. (1993). Practice guidelines: a new reality in drug. III. Impact on patient care. Archives of internal drug 153, 2646-55

[37] Grilli R. L. (1994), Evaluating the message: the relationship between adherence rate and the subject of a practice guideline. Medical care 32, 202-13

[38] Brown E. M., Guidelines for antibiotic usage in hospitals, Journal of Antimicrobial Chemotherapy (2002) 49, 587-592