Dial Traspl. 2010;31(3):89–100

Diálisis y Trasplante

www.elsevier.es/dialis

Clinical practice guidelines

Procedures against dialysis infection

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ARTICLE INFO

Article history:
Received 28 June 2010
Accepted 2 July 2010
Available online 13 August 2010

Keywords:
Guide of clinical practice
Infection
Dialysis
Haemodialysis
Peritoneal dialysis
Medical bibliography
Year 2010

ABSTRACT

An update (year 2010) of Guide of clinical practice of the Spanish Society of Dialysis and transplants is realised on the attitudes against infection in dialysis; 31 points are agreed upon, of which 17 talk about haemodialysis, 11 talk about peritoneal dialysis and 3 about common aspects of the two techniques of dialysis, all with medical bibliography.

Actitudes frente a la infección en diálisis

Palabras clave:
Guía de práctica clínica
Infección
Diálisis
Hemodiálisis
Diálisis Peritoneal
Bibliografía médica
Año 2010

RESUMEN

Se realiza una actualización (año 2010) de la Guía de práctica clínica de la sociedad española de diálisis y trasplante sobre las actitudes frente a la infección en diálisis. Se han consensuado 31 puntos, de los cuales 17 se refieren a la hemodiálisis, 11 se refieren a la diálisis peritoneal y 3 a aspectos comunes de las dos técnicas de diálisis, todos con bibliografía médica.

Introduction

Infectious processes are one of the most frequent complications in chronic renal insufficiency, without underestimating other conditions that are no less important such as cardiovascular, anaemia and osteodystrophy.

Infection, in anybody's life and whatever its origin or location, usually occupies a fundamental protagonism due to its repercussion on daily life, given the limitations conditioned by a high temperature that is frequent in microbial infection or in its absence and the perception of a physical condition with evident decline. This is one of the main reasons why the public, from infancy to old age, is obliged to go to the doctor's surgery or a hospital.

The reason for these guidelines is to be able to review, in a practical way and in specific paragraphs, what have been considered as the most dominant disorders or even those that because of their repercussion, even with lesser importance, bring about worries before taking medical decisions. We have concentrated on the area of chronic renal insufficiency in dialysis patients because of their special characteristics and the adequacy of the dose or pharmacological inconveniences that are inherent to their condition and yet are not applicable to the rest of the population. They present infectious complications (respiratory,

DOI of original article: 10.1016/j.dialis.2010.07.004
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doi:10.1016/j.dialis.2010.07.003

renal, abdominal, cutaneous) similar to those suffered by the rest of the general public, however with a difference that they already have a base or different foundation, as is chronic renal insufficiency, which conditions the response to the infectious aggression because the capacity of defence is lesser on having reduced immunity and therefore makes them more vulnerable.

Infection causes an important level of morbidity in the group of people who must undergo substitutive treatment, since according to statistics, 2 out of each 5 hospital admissions are due to infections. On examination of a sample of 275 patients in a cross section in 2003, this reflected an average of 0.6 admissions/patient/year, of which 40% were due to infection and in diabetics this ratio should be multiplied by 2.5. These data indicate the importance of the impact of this disorder as far as morbidity is concerned and whose mortality was 13% (in the literature examined this varies between 10% and 40%), exceeded only by cardiovascular infections.

There will without a doubt be discrepancies concerning personal experiences or protocols that are used, but in our daily work it is usual to have more than one therapeutic options available for each illness, for which reason we must choose the most appropriate in each case among various that are published consensually. Future knowledge must modify, if necessary, the decisions made in each of the paragraphs or guidelines.

Haemodialysis (HD)

Guideline 1

Prophylaxis measures are effective in preventing spontaneous or transmitted infections. Corporal hygiene is essential, especially around the access area. Barrier precautions, such as gloves, face masks and waterproof skin dressings are compulsory to avoid horizontal transmission. The use of sterile material and adequate antiseptics is required in any handling of the patient. Health professionals must maximize prophylaxis and preventative measures in any intervention on vascular access for dialysis and maintain adequate training. Screening of nasal colonisation should be carried out on all patients but especially those with catheters. Carriers of nasal staphylococcus, both patients and health professionals, must receive treatment with mupirocin of 2 daily applications for 5 days. Carrier patients of infected skin lesions shall receive the treatment indicated but should cover the area of the lesion.

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Guideline 2

Fever is the main symptom of infection. Fever that appears at the start of or during dialysis allows access-related infection, contamination of the dialysate or fungible material, first use syndrome, hypersensitivity reaction, pyrogenic, haemolysis or an inadequate temperature of the monitor to be ruled out. Fever originating during dialysis makes it necessary to apply the medical procedure of usual diagnosis of location and identification.

Elderly people may experience fever with hardly a high temperature, in which case when presented with toxicity symptoms, an infectious source should be ruled out as a reason for the problem. Concomitant treatment with non-steroidal antiinflammatory drugs (NSAIDs) or analgesics can mask this symptom (Fig. 1).

Fever can appear alone or accompanied by bacteremia, with local symptoms in some area of the body or after instrumental manipulation (drip feeds, catheterisation, blood collection), surgical interventions, wounds, skin or vessel infections. A high fever accompanied by shivering, increase in heart rate, perspiration, hypotension, pain, cephalea and vomiting is a symptom of acute bacteremia, wherefore it is necessary to carry out, whenever possible and before any other treatment, a culture of the biological liquids in order to know the source and possible systematic extension. Afterwards steps must be taken as soon as possible in order to avoid a possible septic shock.

Chronic infection should be suspected in the presence of symptoms that are seen to progress with time, although the illness does not appear as explained for acute processes, symptoms such as low-grade fever, intermittent perspiration (day or night), weight loss, anaemia (poor response to erythropoietin [EPO]), positive PCR, hypoalbuminemia (desnutrition) and poor tolerance to dialysis (Fig. 1 and Table 1) are observed (even if not all of them).

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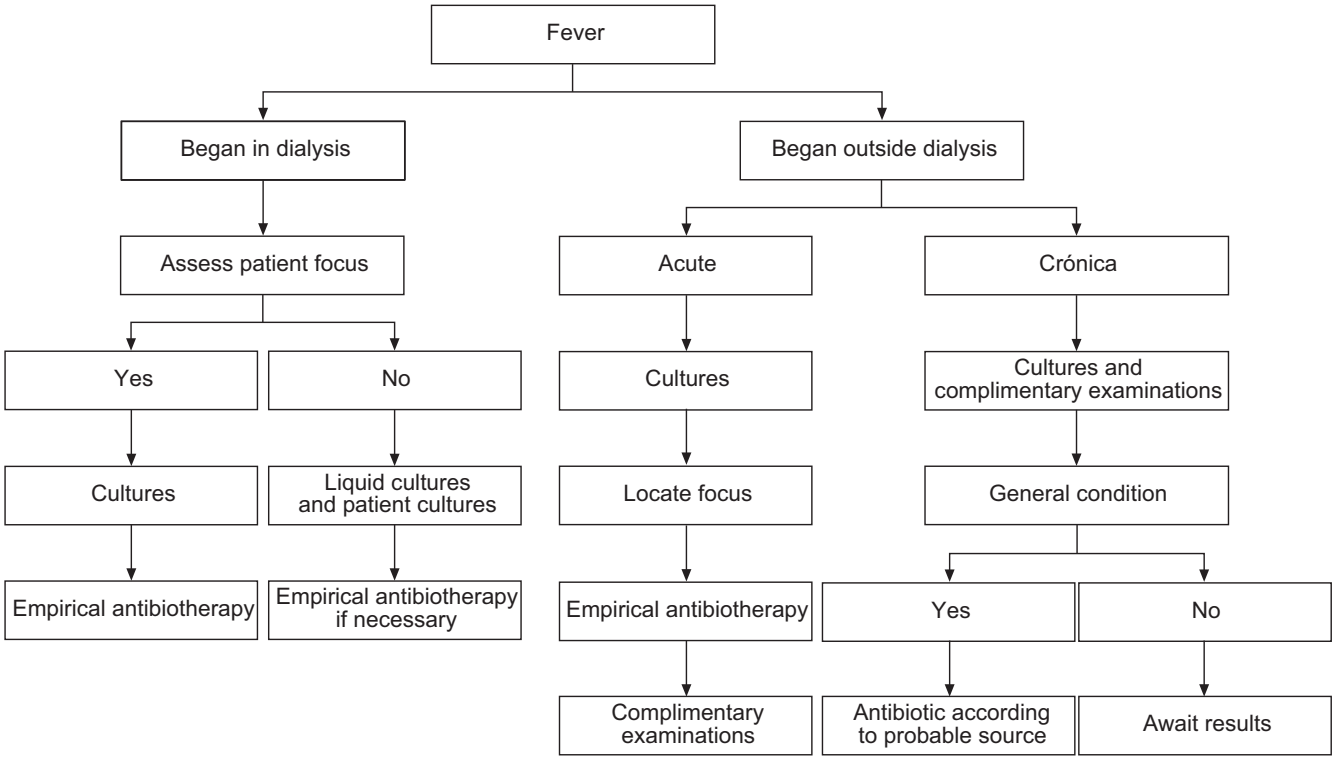

Fig. 1. Diagram of procedure in the case of fever.

Table 1
Difference between acute and chronic infection

Acute infection	Chronic infection
High fever	Low-grade fever
Shivers	Intermittent perspiration
Tachycardia	Weight loss
Perspiration	Anaemia
Hypotension	Positive PCR
Pain	Hypoalbuminemia
Cephalea	Poor tolerance to dialysis
Vomiting	High ferritin level

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Guideline 3

The most frequent microorganisms found in infectious processes are: Gram-negative bacilli (50%), Gram-positive cocci (40%), anaerobes (5%) and others (5%). In cases of nosocomial infection a higher prevalence of Gram-negative germs is observed, with greater resistance to antibiotics (Table 2).

The most frequent location of infection in dialysis patients is found in this order: dialysis access (38%), in which 75% are through the catheter; reno-urological (20%); respiratory tracts (18%); abdomen (9%) and other localities (15%).

Those multiple germs that because of their frequency are the most common in the cultures of our patients shall be explained in detail and others which, although less frequent, require a possible specific treatment or isolation.

If infection is suspected due to local aspect (signs of inflammation or secretion) or general (fever. etc.), clinical

Table 2
Microorganisms involved in infectious processes

Gram-positive bacteria	Gram-negative bacteria
Staplylococcus aureus, *S. epidermidis*	*Escherichia coli*
Methicillin-resistant S. aureus	*Klebsiella*
Enterococcus	*Proteus*
Streptococcus	*Haemophilus*
S. pneumoniae	*Enterobacter*
Bacillus	*Pseudomonas aeruginosa*
Clostridium	*Serratia*
Corynebacterium	*Salmonella*
	Citrobacter
	Legionella
	Acinetobacter
Other pathogens	
Mycoplasma	*Chlamydia*
Fungi	
Candida	*Aspergillus*

criterion of confirmation and localisation shall be established and an etiological hypothesis is necessary based on the medical history, location and background.

If staphylococci infection is suspected, since there is a high rate of resistance to methicillin in dialysis patients, empirical treatment with daptomycin shall be administered. This is the same or more efficient and less toxic than vancomycin and unlike the latter, is as efficient as Cloxacillin against staphylococci sensitive to methicillin (SSM). SEIMC and SEQ treatment Guidelines recommend this.

If Gram-negative bacilli is suspected, third generation Cephalosporin is recommended with or without an aminoglycoside (Table 2).

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Guideline 4

For treatment of methicillin-resistant *S. aureus* or coagulase-negative *Staphylococcus*, daptomycin or vancomycin are recommended but only when the MIC for this second antibiotic is less or equal to 1; if greater than 1, daptomycin is recommended.

If the addition of aminoglycoside is considered, it is advisable to combine it with daptomycin in order to avoid possible nephrotoxicities that may appear if combined with Vancomycin.

If a fungus infection is suspected (usually *Candida albicans*), the use of *an adjusted dose of fluconazole* is recommended.

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Guideline 5

In cases of an allergy to beta-lactams, when neither Cloxacillin nor first generation cephalosporins can be used, the use of daptomycin is recommended instead of vancomycin, since daptomycin is an anti-staphylococcus just as efficient as beta-lactams.

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Guideline 6

If an internal arteriovenous fistula infection is suspected, either autologous or due to a prosthesis, we should anticipate 2–3 weeks of treatment, intravenously and following dialysis.

In the case of tunnel catheters, the same treatment as mentioned earlier is proposed, in the absence of a serious medical condition or lack of response 72 h after applying the treatment.

Withdrawal of the access is proposed in the case of septic shock and in the case of a history of valvulopathy or clinical suspicion of fungal infection. In circumstances of clinical stability, the withdrawal shall be decided after a lack of response after 2–3 weeks.

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Guideline 7

The incidence of bronchopulmonary infections as complications in haemodialysis patients is high and increased because many of these patients already have previous bronchopulmonary conditions together with their renal insufficiency, the most common produced by Gram-positive microorganisms, although it is also necessary to think of *Haemophilus*, *Pseudomonas* and *Legionella.* Empirical treatment should consider these possibilities. For pneumonia acquired in the community Levofloxacin monotherapy is recommended or the combination of beta-lactam (Amoxicillin-Clavulanate or Ceftriaxone) with Azithromycin. For the exacerbation of COPD the same treatment can be applied but if the patient is colonised by *Pseudomonas aeruginosa*, an active beta-lactam must be used against this pathogen (Ceftazidime, Cefepime, Piperacillin-Tazobactam, Meropenem or Doripenem).

The treatment should be maintained between 10 and 20 days.

It is advisable to recommend the administration of the anti-pneumococcal vaccine to all patients.

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Guideline 8

An endocarditis should be considered in the persistence of fever without apparent focality or following an acute process.

70% of the colonisations are produced in the tricuspid valve by *S. aureus* and *Streptococcus viridans*, those caused by enterococcus are less frequent. It is most important to demonstrate endocarditis by means of haemocultures and echocardiogram.

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Guideline 9

Empirical treatment of endocarditis should be carried out according to the SEQ and SEIMC guidelines: daptomycin with a dose of 10 mg/kg of body weight. The addition of aminoglycosides or rifampicin may be considered although not until endocarditis has been confirmed.

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Guideline 10

The urinary tracts are a source of frequent infection due to these patients' own uro-renal conditions and through the lack of sufficient urinary fluid. Cystitis and pyelonefritis, in general, and prostatitis in males are the most common. *Escherichia coli*, *Proteus*, *Klebsiella*, *Enterococcus*, *Pseudomonas* and *Serratia* are the most predominant. The culture of biological liquids is obligatory (urine and blood).

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Guideline 11

If the infection is local empirical treatment should be started with second or third generation cephalosporin or amoxicillin-clavulanate.

If the infection is complicated, treatment should be started with ertapenem in order to cover the enterobacterium producers of extended spectrum beta-lactamases (ESBLs) or if *P. aeruginosa is suspected*, ceftazidim, piperacilina-tazobactam, meropenem or doripenem should be used.

If the infection (urinary) is caused by enterococcus, vancomycin or daptomycin should be considered according to the clinical condition of the patient (immunosuppressive, elderly, diabetics).

The treatment should be continued between 7 and 14 days according to whether the infection is local or complicated and 21 days if there are positive haemocultures.

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Guideline 12

Osteoarticular infections usually stem from embolisms of another septic source or from a direct lesion or ulcera in one of the osseous or articulated areas. The germs found may be varied. Therefore we should study and culture the liquid of the affected articulation and the haemocultures. The need for complimentary serological tests should also be assessed.

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Guideline 13

For empirical purposes, if Gram staining is available and Gram-positive is detected, then treatment with Cloxacillin or first generation cephalosporin is recommended and if penicillin is incompatible, then daptomycin should be used.

If a Gram-negative bacillus is discovered in the Gram staining, treatment with third generation Cephalosporin is recommended.

Vancomycin is not recommended in cases of articular prosthesis infections due to its poor penetration in biofilms and toxicity in prolonged treatment that is required for these infections.

At present daptomycin is the best drug for eliminating biofilms and in animals has proved to be superior compared with vancomycin in prosthesis infections. The treatment should be prolonged for at least four weeks.

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Guideline 14

Intra-abdominal infection is generally produced by enterobacteria, *Enterococcus* and anaerobic bacteria. The origin is established mainly in a torn hollow viscus and to a lesser percentage by hematogenous tract, bacterial translocation and others.

Infectious complications of the peritoneal dialysis are not included here but are described in detail in Guidelines 18–28.

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Guideline 15

Once the cultures for identification have been prepared, empirical dosage should be started with Amoxicillin-Clavulanate, third generation Cephalosporin with Metronidazole, Ertapenem, daptomycin, tigecycline or teicoplanin.

In those patients who cannot be treated for enterococcus with either ampicillin or aminoglycoside, the use of daptomycin is recommended. Vancomycin should be avoided due to deterioration of the residual renal function and linezolid due to possible accumulation of unleashed metabolites of lactic acidosis.

The dosage of antibiotics should be modified following an assessment after 48–72 h or when the results of the culture are known. For fungal infections due to *Candida*, Fluconazole should be used or a Candin (Caspofungin, Anidulafungin or Micafungin).

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Guideline 16

Tuberculosis is an infection that still occurs in dialysis patients (10 times superior than in the general population); therefore it would be convenient to carry out a test (PPD), especially in those patients with fever of unknown source, weight loss, desnutrition, less obvious pleural effusion or pulmonary infiltration, adenopathies, ascites or hepatomegalies. Extrapulmonary localisation is frequent. A negative PPD does not exclude it.

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Guideline 17

The treatment should be administered with the usual dosage: rifampicin, isoniazid and pyrazinamide, adding ethambutol in cases of suspected resistance, during the first 2 months. Isonazid and rifampicin shall be continued afterwards to be completed during 9–12 months.

Rifampicin should always be administered on an empty stomach. Isoniazid and rifampicin require no dose modification in case of renal insufficiency but must be administered after haemodialysis.

In cases of relapse or incomplete previous treatment, a dosage with 4 drugs should be carried out in the first 2 months in case of resistance. It is advisable to add pyridoxine.

The impossibility of using triple therapy in the first 2 months, due to intolerance to one or several of the antibiotics, determines the search for a double combination, which allows it to be maintained during 18 months. The combination of pyrazinamide+levofloxacin would be useful in cases where it is impossible to prescribe rifampicin, isoniazid or ethambutol.

Those patients with a previously negative PPD, who seroconvert in dialysis or who have an induration >10 mm, must be prescribed prophylactic treatment during 6 months. It would also be advisable in cases of negative PPD in contact with an active carrier.

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Peritoneal dialysis (PD)

Guideline 18

The patient receiving peritoneal dialysis has specific infections: related to the catheter or peritonitis.

Prophylactic measures mentioned in Guideline 1, such as the administration of intravenous antibiotic in the insertion of the catheter, cefazolin or vancomycin1, have to be implemented afterwards with hypertonic saline solution wash of the orifice of the peritoneal catheter. Hydrogen peroxide should be specifically avoided. The search for and treatment of nasal carriers is important.

Guideline 19

Infection should be suspected in the case of signs of periorificial flogosis: tumor, blushing, pain and especially sweating (related to the catheter), suspicion of subcutaneous abscess, cloudy peritoneal liquid or abdominal pain (peritonitis) with or without fever.

Guideline 20

If an infection of the orifice is suspected (a possibility if there is erythema and certainly if there is purulent secretion), local prophylaxis should be reinforced with washes of hypertonic saline solution and an application of 2% mupirocin cream or gentamicin. If there is no response after 48–72 h, it is necessary to use the specific antibiotic for the isolated germ. If biological data are not available, other drugs of a broader spectrum have to be used, such as topical ciprofloxacin or bacitracin until the antibiogram is known. If there is secretion, the treatment should be carried out through systematic administration (Table 1).

Guideline 21

If a tunnel infection is suspected (secretion and/or edema and/or pain on touch), normally preceded by infection of the orifice and after proceeding to bacteriological studies, a local and systematic empirical treatment should be administered, initially orally (Table 3), according to the results of the Gram staining of cutaneous smear or the secretion, if this technique were feasible, according to the indications in Guideline 4. The confirmation of the germ and its sensitivity implies changing the treatment if necessary. These treatments should have a minimum duration of 14 days. It is especially important to identify *Staphylococcus aureus and/or P. aeruginosa*, since the duration of the antibiotic treatment may be prolonged with these germs.

Table 3
Treatment of infection of the orifice/tunnel[2]

Name of the antibiotic DCPA	Dosage
Amoxicillin	250–500 mg/12 h
Cephalexin	500 mg/12 h
Ciprofloxacin	250–500 mg/12 h
Clarithromycin	250–500 mg/12 h
Daptomycin	6 mg/kg/day
Dicloxacillin	250–500 mg/12 h
Fluconazole	200 mg/day
Isoniazid	2000 mg first day, then 1000 mg/day
Linezolid	600 mg/12 h
Metronidazole	400 mg/12 h, <50 kg 400–500 mg/8 h, >50 kg
Ofloxacin	400 mg first day, then 200 mg/day
Pyrazinamide	35 mg/kg/day
Rifampicin	450 mg/day, <50 kg 600 mg/day, >50 kg
Trimethoprim/sulfamethoxazole	80/400 mg/day

Guideline 22

The appearance of peritonitis or if the infection remains after 4 weeks implies the withdrawal of the catheter (Table 3).

Guideline 23

If peritonitis is suspected (basically a cloudy liquid) and after the cytological assessments (more than 100 cells/ml, with 50% being polymorphonuclear) and bacteriologic (carrying out of culture and recommended Gram staining) of the effluent, intraperitoneal treatment should be administered with vancomycin and a beta-lactam with activity against pseudomonas. Synergic action can be achieved by adding tobramycin.

Gram staining can not only provide bacterial data but also give an early warning of fungi. See dose in Table 3.

Guideline 24

When peritoneal infection is confirmed and the germ identified as Gram-positive, the treatment can be adjusted to the sensitivity of the causing agent or vancomycin can be maintained if the response has been favourable.

In the case of Gram-negative confirmation, vancomycin should be withdrawn and the treatment continued with a beta-lactam adequate for sensitivity. If the isolated pathogen is *P. aeruginosa*, a treatment combined with aminoglycoside is advisable in order to search for synergy. In the case of allergy towards beta-lactams, ciprofloxacin can be used whenever *P. aeruginosa* is sensitive.

See dose in Table 3.

Guideline 25

If peritonitis is confirmed by methicillin-resistant *Staphylococcus aureus and* if the empirical response to Vancomycin has not been satisfactory, then the introduction of daptomycin can be considered.

Guideline 26

Other recommendations to be taken into account:

- If peritonitis is suspected through anaerobic germs (e.g. perforation), the addition of metronidazole and ampicillin is recommended. However, if it is polymicrobial, then a surgical assessment is advisable.
- In the case of peritonitis in APD, treatment is advised over longer intervals and with larger doses or frequency (Table 4).
- It is advisable to adjust the dose according to body weight, residual function and also in high transporters.

Guideline 27

If fungal peritonitis is confirmed, usually due to *Candida*, fluconazole or candin should be indicated, separately or together, either through systemic administration or peritoneal and early withdrawal of the catheter should be carried out, although some authors advise waiting 48–72 h for a response to the treatment.

Guideline 28

In any type of peritonitis a lack of response after 5 days or at most after a week of treatment or a worsening of the condition should indicate the withdrawal of the catheter. In this case, it is advisable to maintain the antibiotic treatment for at least 7 days after withdrawal of the peritoneal catheter.

Common features (HD and PD)

Guideline 29

Isolation criteria:

- Pulmonary tuberculosis in active phase, during the first 2 weeks of withening treatment.
- Systematic infection or open suppuration due to methicillin-resistant *S. aureus*. The nasal carriers of this microorganism do not need isolation, but should receive treatment with mupirocin and a strict adherence to all the measures indicated in "Guideline 1". If there are cutaneous lesions positive to methicillin-resistant *S. aureus*, these should be protected during the stay in the dialysis unit.
- Patients with acute bronchopulmonary infection due to *Acinetobacter and/or Aspergillus*.

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Guideline 30

Faced with a situation of acute infection and also in the case of chronic haemodialysis infection (Fig. 2), it is necessary to adjust the doses of the following drugs: amoxicillin-clavulanate 500/125/24 h, with additional dose after dialysis; aztreonam 1 g/24 h and 500 mg after dialysis; cefazolin 1 g/24 h and 500 mg after dialysis; cefuroxime 750 mg/24 h intravenous, with additional dose after dialysis; cefuroxime 500 mg/24 h orally; ceftazidime 500 mg/24 h, with additional dose after dialysis; ciprofloxacin 500 mg/24 h, with additional dose after dialysis yet not at the same time as calcium salts or Fe; cloxacillin 2 g/8 h; ethambutol 15 mg/kg/48 h, flucytosine 37.5 mg/kg/48 h; fluconazole 200 mg/24 h; gentamicin 2 mg/kg/48 h after dialysis, levofloxacin 500 mg initially and 125 mg/24 h not at the same time as calcium salts or Fe; rifampicin 300 mg/24 h; vancomycin 1 g/week; pyrazinamide no data (assess the need for treatment).

Guideline 31

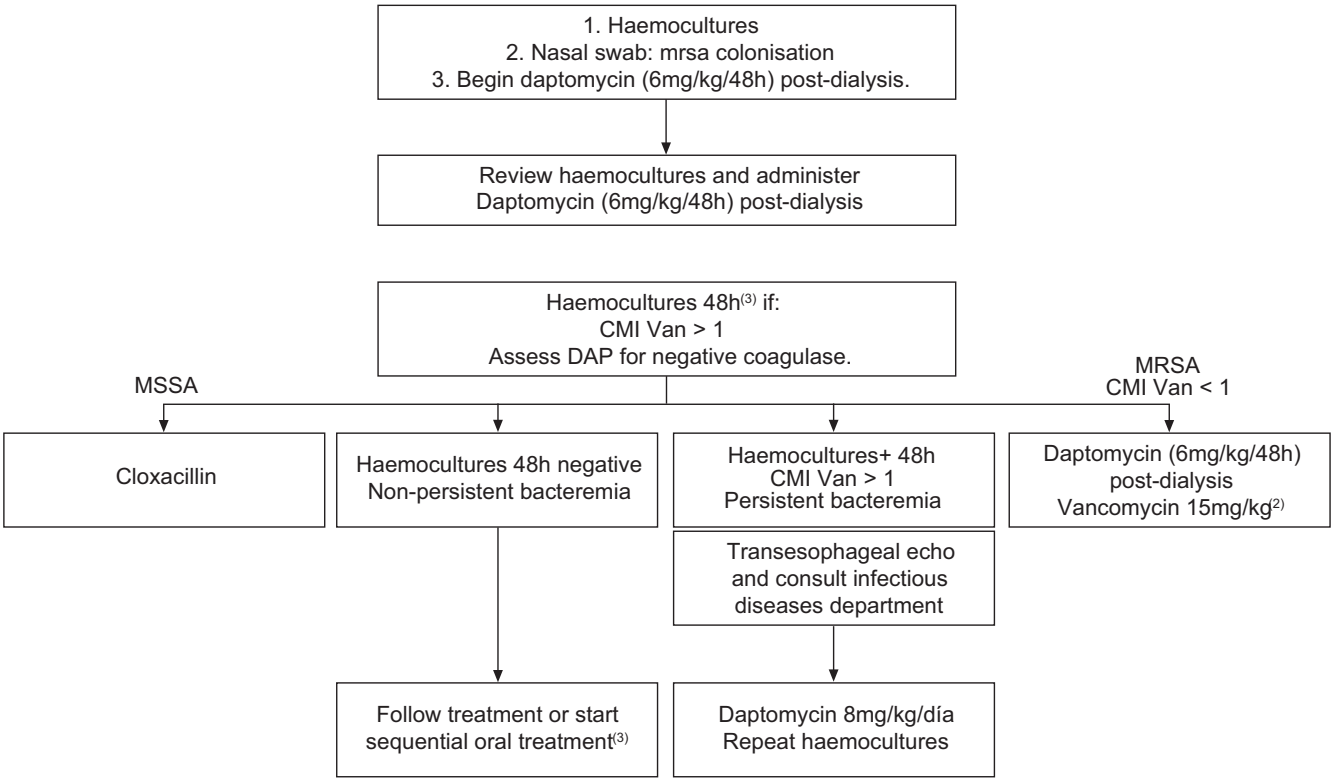
Due to their own specific toxicity, possible organic or systematic manifestations associated with the anti-infectious treatment must be monitored. Therefore, attention must be paid to:

- beta-lactams—reactions of systemic hypersensitivity, fever;
- cephalosporins—possibility of allergies and occasionally encephalopathy;

Table 4
Antibiotic treatment for peritonitis

Name of antibiotic CAPD	Intermittent (1 booster shot/day)	Continues (load/l)	Continuous (maintenance)
Amoxicillin	ND	250–500	50
Ampicillin	ND	125	125
Amikacin	2 mg/kg	25	12
Tobramycin or Gentamicin	0.6 mg/kg	8	4
Cefazolin or cephalothin	15 mg/kg	500	125
Ceftazidime	1000–1500 mg	500	125
Cefepime	1000 mg	500	125
Ciprofloxacin	ND	50	25
Vancomycin	15–30 mg/kg every 5–7 days	1000	25
Aztreonam	ND	1000	250
Imipenem/cilastatin	1000 mg (2 booster shots/day)	500	200
Quinupristin-Dalfopristin	25 mg/l (alternate booster shots)	ND	ND
Amphotericin B	ND	ND	1500
Ampicillin-sulbactam	2000/every 12 h	1000	100
APD			
Vancomycin	30 mg/kg long perm./3–5 days		15 mg/kg lp/3–5 days
Cefazolin	20 mg/kg lp/days		
Tobramycin	1.5 mg/kg long perm./day		0.5 mg/kg lp/day
Cefepime	1000 mg/day		
Fluconazole	200 mg/day every 24–48 h		

APD: acute PD; CAPD: continuous ambulatory peritoneal dialysis.



(2) adjust to trough level 15-20
(3) haemocultures need to be repeated every 48h until 2 negative series

Fig. 2. Patient with chronic renal insufficiency in haemodialysis programme. Medical profile compatible with bacteremia without apparent source.

- ethambutol—ocular alterations, hyperuricaemia;
- flucytosine and fluconazole—digestive problems, cutaneous reactions, alterations of the central nervous system, elevation of the transaminases, medullar toxicity;
- gentamicin—toxicity of pair VII, the other aminoglycosides are less toxic (tobramycin, amikacin);
- isoniazid—peripheral neuritis (avoidable if pyridoxine is added) hepatotoxicity in the first months;
- linezolid—do not administer with MAOIs, do not give orally to patients with phenylketonuria, neuropathy;
- metronidazole—digestive problems and cutaneous reactions in prolonged treatment (sensitive polyneuritis, encephalopathy, convulsions);
- pyrazinamide—photosensitivity, hepatotoxicity, hyperuricaemia, porphyria;
- quinolone—athralgias, photosensitivity, alterations of the central nervous system;
- rifampicin—ataxia, myopathy, cephalea, photosensitivity, increase of bilirubin, flu syndrome administered intermittently;
- vancomycin—red man syndrome, (skin *rash* if not administered slowly), reversible leukopenia and thrombocytopenia;
- amphotericin B—pain on intraperitoneal infusion.

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Conflicts of interest

The authors declare no conflicts of interest.