

Causes of fever in dialysis patients and its treatment

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Abstract

Introduction

There are various types of fevers of unknown origin (FUO) among dialysis patients. Physicians should determine the causes of fever and start providing patients with appropriate treatment as early as possible. The aim of this review was to discuss the causes, diagnosis and treatments of FUO in dialysis patients.

Discussion

FUO is classified into four types depending on the patients' background: classical, nosocomial, neutropenic, and human immunodeficiency virus (HIV)-associated FUO. Haemodialysis patients may develop a fever as an allergic reaction to a dialysis circuit. Therefore, various items including dialysis membranes, dialysis circuits, puncture needles, anticoagulants, and endotoxin should be examined. The main pathogenic mechanism underlying the development of FUO in dialysis patients is based on allergic reactions to the materials used in dialysis devices and the contaminants (endotoxins) in the dialysate. When the cause of fever is unclear, diagnosis should be started on the basis of the urgency of treatment and the classification of FUO to provide appropriate treatment. When an allergic reaction to the materials used in dialysis devices is suspected, such materials and the sterilization method should be examined to determine the causes of fever and be replaced with a device made of other materials or another method as necessary.

Conclusion

There are various causes of fever in dialysis patients. The identification of

the causes of fever and its appropriate treatment based on the severity of the symptoms are essential for dialysis patients with FUO.

Introduction

Fever is a symptom that physicians frequently encounter in dialysis patients in clinical settings. There are various types of diseases accompanied by fever, for example, infectious diseases, malignancies, and allergies. Because dialysis patients tend to have a weakened immune system because of aging or complications of diabetes, infectious diseases may become severe and sometimes become fatal.

Blindly assuming the cause of fever to be an infection will delay the administration of necessary treatments. Therefore, physicians should determine the causes of fever and start providing patients with appropriate treatment as early as possible. In this review, we discuss the causes, diagnosis and treatments of FUO in dialysis patients.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Fever of unknown origin (FUO)

According to a report by Petersdorf and Beeson published in 1961, the criteria for FUO are as follows: (i) a duration of fever ≥ 3 weeks, (ii) a temperature higher than 38.3°C on several occasions, and (iii) undiagnosed after 1 week of inpatient examination¹. Namely, FUO is a fever that does not resolve even after a

certain period and cannot be diagnosed by detailed examination in medical institutions. FUO defined by Petersdorf and Beeson is now considered classical FUO as explained below.

Table 1 shows the classification of FUO proposed by Durack and Street². FUO defined by Petersdorf and Beeson is considered as classical FUO. In addition, FUO is also classified into three other categories depending on the patients' background: FUO in inpatients with acute disorder or postoperative patients (nosocomial FUO), FUO in patients with neutropenia due to chemical therapy (neutropenic FUO), and FUO in human immunodeficiency virus (HIV)-infected patients (HIV-associated FUO). The fever duration differs among these types of FUO: 3 weeks for classical FUO, 3 days for nosocomial and neutropenic FUO, and 4 weeks for HIV-associated FUO. This difference comes from the classification of FUO in patients with different historical backgrounds, and the urgency and method of treatment differ. For example, neutropenic FUO after chemical therapy may become fatal in a short period and it requires treatment on an hourly basis.

Causes of fever

The common causes of fever in nondialysis patients are infectious diseases, malignancies, and connective tissue diseases. In contrast, various causes of fever are considered in dialysis patients because they use shunts and catheters, have an immune system weakened by the complications of diabetes or the use of steroids, and undergo regular dialysis sessions (Table 2)³.

Infection is the most common cause of fever in dialysis patients; in particular, the prevalences of infections of the respiratory system, the dialysis access site, and the urinary tract are high³. The causative bacteria vary from gram-positive to gram-negative. Methicillin-

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resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and pathogenic fungi may cause infection and therefore fever in dialysis patients because of their weakened immune system.

Tuberculous infection should also be considered. The prevalence of extrapulmonary tuberculosis (i.e., military tuberculosis, lymph nodes, kidneys, urinary tract, and pleura) is higher among dialysis patients than among healthy people. The detection rate for the tuberculosis bacterium and the percentage of patients with a positive tuberculin skin test result among dialysis patients are low, which makes a definite diagnosis difficult. Haemodialysis patients use a vascular access for dialysis and attention should be paid to access-related infections^{4,5,6}.

Moreover, haemodialysis patients may be infected by pathogens via the artificial blood vessel or the puncture or insertion site of a dialysis catheter. For peritoneal dialysis patients, exit-site and tunnel infections may occur in a peritoneal dialysis catheter, resulting in peritonitis. A Spanish report showed that approximately 6% of peritonitis patients died⁷. Other studies showed that the peritonitis-related mortality in peritoneal dialysis patients ranged from 3.5 to 5%^{8,9}. Patients on haemodialysis or peritoneal dialysis have a high risk of death from infection because of their use of a catheter as an artificial blood access; thus, they require prompt treatment^{10,11}.

Care should also be taken to malignancy-associated fever because many dialysis patients have malignancies in the digestive and urinary organs^{12,13}. Renal cancers have been increasingly detected by abdominal ultrasonography or computed tomography (CT) rather than after the manifestation of symptoms such as haematuria and low back pain. Blood tumours such as malignant lymphoma and leukaemia may also cause a fever.

Connective tissue diseases have already developed as primary diseases in many dialysis patients and rarely develop as new diseases.

Table 1: Classification of FUO proposed by Durack and Stree.

Classification	Definition	Main causes
Classical FUO	(1)Fever ≥ 38.3 °C for a duration ≥ 3 weeks (2)Undiagnosed after appropriate examination during ≥ 3 outpatient visits or ≥ 3 days in hospital	Infectious diseases, malignancies, connective tissue diseases
Nosocomial FUO	(1)Infection not present on hospital admission (2)Fever ≥ 38.3 °C on several occasions during hospitalization (3)Diagnosis not determined after 3 days of appropriate examination including at least 2 days of incubation period of culture	In-hospital infection, postoperative infection, drug fever
Neutropenic FUO	(1)Neutrophil count $< 500/\mu\text{L}$ or expected to fall to $< 500/\mu\text{L}$ from $1000/\mu\text{L}$ in a few days (2)Fever ≥ 38.3 °C on several occasions (3)Diagnosis not determined after 3 days of appropriate examination including at least 2 days of incubation period of culture	Infectious diseases, infection after chemical therapy
HIV-associated FUO	(1)HIV-positive (2)Fever ≥ 38.3 °C on several occasions (3)Fever persisting over a period ≥ 4 weeks for outpatients or ≥ 3 days for inpatients (4)Diagnosis not determined after 3 days of appropriate examination including at least 2 days of incubation period of culture	HIV, opportunistic infection (e.g., cytomegalovirus, <i>Toxoplasma gondii</i> , <i>Pneumocystis carinii</i>)

However, stabilized primary diseases may recur with fever.

Drug-induced fever (drug fever) is a hypersensitivity reaction to a drug administered to patients^{14,15}. Many dialysis patients are administered multiple drugs and hence tend to develop drug fever. Symptoms of drug fever, including chills, muscle pain, rash (maculopapular skin rash), and headache, generally manifest in approximately 7-10 days after the start of drug use¹⁶. An increase in eosinophil count may be observed in blood examinations. For patients who have neither infection- nor noninfection-related causes of fever, when their fever goes down within 72 h after the withdrawal of the suspected causal drug, their fever should be diagnosed as drug fever.

Drugs that easily cause a fever include antibacterial drugs (penicillin, cephalosporin, and amphotericin B),

anticancer drugs (interferon and gemcitabine), and drugs acting on the central nervous system (phenytoin). Haemodialysis patients may develop a fever because of an allergic reaction to a dialysis circuit. Therefore, the effects of dialysis-related items such as dialysis membranes, dialysis circuits, puncture needles, anticoagulants, and endotoxin should be examined. The time course of fever should be checked because the fever may be observed in association with dialysis.

The main pathogenic mechanism underlying the development of dialysis-related fever is based on allergic reactions to the materials used in dialysis devices and the contaminants (endotoxins) in the dialysate.

Patients on haemodialysis may develop a fever as an allergic reaction after blood comes into contact with a dialysis device as an artificial material¹⁷. When patients develop an

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allergic symptom such as anaphylactic shock within a few minutes after the start of dialysis (type A), substances from the dialyzer or bacterial contaminants are considered as a cause of the symptom. Sterilization using ethylene oxide gas more frequently induces allergic reactions than γ -ray and autoclave sterilizations and requires careful checking. The symptoms of patients with immunoglobulin E (IgE) antibodies against ethylene oxide gas may become serious¹⁸. Drugs administered to dialysis patients, such as anticoagulants (heparin), acetate, and erythropoietin, may also induce a fever¹⁹.

Contaminants in the dialysate such as endotoxins and bacterial components (peptidoglycan) may be absorbed into the patient's body through inverse diffusion or inverse filtration via the dialysis membrane and cause a fever²⁰.

Therefore, regular monitoring of the quality of the dialysate and the appropriate purification of the dialysate are indispensable. Mild allergic symptoms that occur approximately 30 min after the start of dialysis are of type B, which occurs later than type A¹⁷. Type B allergic reactions are considered to result from the activation of the complement system after blood comes in contact with the dialysis membrane²¹. For example, regenerated cellulose membranes used for dialysis tend to activate this complement system. Thus, the material quality of dialysis membranes has been improved and synthetic polymer membranes have been manufactured. In addition to the above-mentioned allergic reactions, the temperature of the dialysate incorporated into dialysis machines may also cause a fever when it is set high.

Diagnosis

When the cause of fever is clear, the appropriate treatment strategy can be promptly taken. When the cause of fever is unclear, however, diagnosis should be started on the basis of the urgency of treatment and Durack and Street's FUO classification. First, the

Table 2: Causes of fever in dialysis patients.

Infectious diseases	Bacteria [respiratory system, urinary tract, peritoneal and intrapelvic abscesses, infective endocarditis, renal and perirenal abscesses, dialysis access site, continuous ambulatory peritoneal dialysis (CAPD) catheter] Tuberculosis (miliary tuberculosis, nephrophthisis) Viruses [cytomegalovirus, Epstein-Barr virus (EBV)] Fungi (<i>Candida</i> , <i>Aspergillus</i>)
Malignancies	Malignant lymphoma, renal cancer, liver cancer and metastatic liver cancer, colon cancer
Connective tissue diseases	Adult-onset Still's disease, temporal arteritis, polymyalgia rheumatic, systemic lupus erythematosus, polyarteritis nodosa, and microscopic polyarteritis
Dialysis-related causes	Dialysis membranes, dialysis circuits, puncture needles, anticoagulants, endotoxin
Others	Drug fever, cirrhosis, deep venous thrombosis

patient's clinical history should be carefully examined. For example, the onset time and time course of fever, the place of cause of fever (inside or outside the hospital), the use of artificial materials (catheters and artificial blood vessels), possible factors for the decrease in neutrophil count, and the risk of HIV infection should be examined. It is also useful to interview the patients about their travel history, living environment, the presence or absence of persons they are in close contact with a similar symptom, regular medication, and pet ownership.

Next, repeated physical examinations should be carried out to monitor the changes in patients with time. In addition to the general physical findings, a close observation for redness, pain, swelling, and drainage at the skin around the blood access of haemodialysis patients and the catheter of peritoneal dialysis patients is essential. Physicians should not indiscriminately order for examinations but anticipate the possible diagnosis that can be inferred from the examination results before making the order. For patients with an allergy to the materials used in dialysis devices, their eosinophil count and IgE level may increase, but increases in white blood cell count and C-reactive protein (CRP) level are rarely observed when such patients have no infections. However, the

white blood cell count and CRP level may increase in patients with a fever owing to contaminants such as endotoxins.

Treatment

Basically, the treatment of FUO in dialysis patients should be started after the cause of FUO is determined. Early administration of antibacterial drugs should be avoided. When patients require no urgent treatment and are in good condition, most cases of fever including those caused by viral infection will resolve as self-limited diseases during the follow-up period. A duration of 3 weeks described in the definition of classical FUO is set for this natural resolution. However, this three-week course may not be true for all patients. When symptoms rapidly worsen and become serious, empiric therapy should be started before the establishment of a definite diagnosis. A basic method is to identify the causal bacterium and administer an antibacterial drug.

For immunocompromised hosts, a broad-spectrum antibacterial drug should be used. Diseases requiring urgent treatment include septicemia, neutropenic FUO, and severe infectious diseases (infective endocarditis, intraabdominal abscess, and pneumonia). When an artificial material such as a dialysis catheter is considered to be the cause of fever, the material should be removed^{4,5,6}.

The Haemodialysis (HEMO) Study showed that 7.6% of all the study patients used a catheter as the vascular access for dialysis and that 32% of the study patients admitted with access-related infection used a catheter⁶. Another study showed that the risk of infection-related death was approximately threefold higher among haemodialysis patients who used a catheter than among those who used an arteriovenous fistula²². If an infection with tuberculosis is suspected, it may be adequate to start empiric treatment before the establishment of a definite diagnosis.

If an allergy to the materials used in dialysis devices is suspected, the materials of the dialysis devices and the sterilization method should be examined to determine the causes of fever and be replaced with a device made of other materials or another method as necessary.

If a dialysis membrane is considered to be a cause of fever, it should be replaced with a more biocompatible dialysis membrane. For contaminants in the dialysate, the dialysate should be purified more carefully and an endotoxin retentive filter should be installed.

For connective tissue diseases, the use of a steroid or an immunosuppressant is generally effective. For malignancies, surgery or chemical therapy should be adopted after the determination of the site and stage of malignancy.

Conclusion

There are various causes of fever in dialysis patients. Basically, early administration of an antibacterial drug or a steroid before the establishment of a definite diagnosis of the primary disease should be avoided because it delays accurate diagnosis. In contrast, infectious diseases due to in-hospital infection or complicated by neutropenic FUO should be urgently treated because they may become severe without prompt and appropriate treatment. The identification of the causes of fever and the appropriate treatment based on the severity of symptoms are

essential for dialysis patients with FUO.

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