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POSTTRANSPLANT FEVER IN CRITICALLY ILL ORGAN TRANSPLANT RECIPIENTS

Patricia Muñoz and Emilio Bouza
Servicio de Microbiología Clínica y Enfermedades Infecciosas. Hospital General Universitario "Gregorio Marañón. Madrid. Spain.

INTRODUCTION

Fever is common in solid organ transplant (SOT) recipients (1). This chapter deals with the etiology, approach and outcome of clinical entities in which fever without an identifiable cause is the major finding. While, patients in the ward may also have severe infections, ICU stay poses unique risk factors for infection. We will therefore focus on fever in context of SOT recipients in the ICU. Our aim is to provide information and guidelines regarding most frequently encountered clinical scenarios relevant to critically ill febrile patients. Where no solid data were available, perspectives based on our own experience and opinion are presented.

1. HOW COMMON IS ICU ADMISSION AFTER SOT AND HOW FREQUENTLY IS IT COMPLICATED BY FEVER?

From 5-50% of SOT candidates await transplantation in an ICU and, after the procedure most of them are re-admitted during a mean of 4-7 days for life support (2-6). However, most ICU days will take place during the period of deepest immunosupression (7).

Figures regarding fever and ICU admission show that one-half of all febrile days in liver recipients occurs in the ICU, and 87% of these are caused by infection (8). Once in the ICU, the risk of infection is particularly high in ventilated patients (53% vs 19%) and in patients

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requiring dialysis (62% vs 22%). This latter group also have more bloodstream infections (38% vs 8%) (7, 9). Admission to ICU also reflects the etiology of the infection. It is more common with lung infections requiring ventilatory support. For instance, 70% of patients with *P. carinii* pneumonia are admitted, while very few CMV diseases require ICU care (10). Finally, the abscence of fever does not exclude infection. In fact, 40% of the liver recipients with documented infection (mainly fungal) were afebrile in a recent series (8).

2. WHAT INFORMATION DO UNDERLYING DISEASE AND TYPE OF TRANSPLANTATION YIELD?

The underlying disease and the type of transplantation are very important determinants of the risk of early and late infections. In heart recipients (HT), patients with prior ischemic cardiomyopathy experience more surgical complications, longer post-operative mechanical assistance and are more susceptible to *P. carinii* pneumonia (11, 12). After orthotopic liver transplantation (OLT), patients with prior fulminant liver disease fared the worst ICU course and cirrhotics the best (13). Following lung transplantation, patients with obstructive lung disease, double lung transplant or cystic fibrosis have had a longer stay in the ICU and a higher risk of infection (3, 14, 15).

The type of SOT determines the complexity of the surgery, the intensity of immunosuppression and the most likely sites of infection. Lung and HT recipients are especially susceptible to thoracic infections, whereas intra-abdominal complications predominate in OLT or pancreas recipients. Certain infections are characteristic of a particular type of transplantation, e.g. infections related to circulatory support devices (intra-aortic balloon pumps, ventricular assistance devices and total artificial hearts) in heart transplant recipients (16-18). Infections such as insertion site sepsis, endocarditis, pneumonia, candidiasis or sternal infection may complicate 38% of support courses.

3. WHAT HISTORICAL DATA SHOULD BE SOUGHT IN THE PATIENTS?

Risk factors for infection should be carefully sought in all febrile patients.A careful anamnesis should check for risk factors for

infection. The pretransplantation history e.g. serological status against microorganisms such as CMV, hepatitis virus, *Toxoplasma*, etc may yield valuable information. Previous infections or colonization, exposure to tuberculosis, contact with animals, raw food ingestion, gardening, prior antimicrobial therapy or prophylaxis, vaccines or immunosuppressors and contact with contaminated environment or persons should be recorded (19). History of residence or travel to endemic areas of regional mycosis or *S. stercoralis* may be essential to recognize these diseases (20).

Certain complications may increase the risk of bacterial and fungal infection in the early posttransplant period. Them include long operation (over 8 h), blood use in excess of 3 l, allograft dysfunction, pulmonary or neurological problems, diaphragmatic dysfunction, renal failure, hyperglycemia, poor nutritional state and thrombocytopenia (13, 21-24). Intra-operative hypothermia increased the incidence of early cytomegalovirus infection in liver transplant recipients (25)

4. COULD PHYSICAL EXAMINATION ELICIT OBJECTIVE CLUES AND PREVIOUSLY OVERLOOKED FINDINGS?

Fever in critically ill transplant recipients should be considered an emergency. In our opinion, a basic tenet of the management of a SOT with fever is that physical examination data should be directly obtained by the ID consultant, not relying on second hand information. This may be more useful than many expensive and time-consuming tests.

The oral cavity is frequently forgotten and may disclose previously unnoticed herpetic gingivo-stomatitis or ulcers. Within the exploration of the thoracic area, the consultant should visualize the entry sites of all intravascular devices, even if they "have just been cleansed". It should be remembered that the presence of inflammatory signs is suggestive of infection, although their absence does not exclude infection. Sepsis, without local signs, may be the initial sign of postsurgical mediastinitis. When the sternal wound remains closed, a positive epicardial pacer wire culture may be a clue to sternal osteomyelitis (26). Although unusual after SOT, cardiac auscultation and echography may help to detect endocarditis (27) and physical examination may occasionally disclose the existence of pneumonia or empyema before abnormal radiological signs become evident.

The abdominal examination is always essential, especially in OLT recipients. The surgical wound is also a common site of infection and a cause of fever. Its presence requires rapid debridement and effective antimicrobial therapy and should prompt the exclusion of adjacent cavities or organ infection. If ascites is present, it should be immediately analyzed and properly cultured to exclude peritonitis. We recommend bedside inoculation in blood-culture bottles due to its higher yield of positive results. Examination of the iliac fossa is particularly important after kidney transplantation. Tenderness, erythema, fluctuance or increase in the allograft size may indicate the presence of a deep infection or rejection. Ultrasound or CT-guided aspiration may facilitate the diagnosis. The possibility of colonic perforation in steroid–treated patients or gastrointestinal CMV disease should always be considered in intraabdominal infections.

Finally, skin and retinal examination are "windows" at which the physician may look in and obtain quite useful information on the possible etiology of a previously unexplained febrile episode. We have analyzed the value of ocular lesions in the diagnosis and prognosis of patients with tuberculosis, bacteremia and sepsis (28, 29). Cutaneous or subcutaneous lesions are a valuable source of information and frequently allow a rapid diagnosis. Viral and fungal infections are the leading causes of skin lesions in this setting. The entire skin surface should be inspected and palpated in SOT recipient with unexplained fever. The biopsy of nodules, subcutaneous lesions or collections may lead to the immediate diagnosis of invasive mycoses and infections caused by *Nocardia* or Mycobacteria, among others.

5. DOES CHRONOLOGY AFTER SOT HELP IN FINDING THE CAUSE OF FEVER WITHOUT A CLEAR ORIGIN?

An aggressive diagnostic approach is necessary when dealing with febrile compromised ICU hosts since it has been shown or documented that many infectious complications remain undiagnosed. In a recent study, complete agreement between pre and post mortem diagnoses took place in only 58% of a total 149 patients. Two thirds of all missed diagnoses were infectious and disagreement was particularly prominent in the transplant population (complete agreement 17% and major error in 61%) in comparison with trauma patients (complete agreement 86%) or cardiac surgery group (69%). The majority of the missed diagnoses were fungal infections. Longer ICU stays increased the rate of error (28).

Approximately 25% of febrile episodes do not present with an evident focal origin and do not permit a straight syndromic approach (29). Therefore, the patient's antecedents, type of transplantation and time after surgery are essential. We systematically recommend to our residents to go over the viral, bacterial, fungal and parasitic etiologies that should be excluded.

All SOT recipients share a number of conditions (end-stage organ failure, surgery, immunosuppressive regimens, etc) that bring along a predictable time line of post-transplant infectious complications. In the first month after SOT, patients are very susceptible to bacterial complications such as ventilator-associated pneumonia, IV catheter-related infections, surgical wound infection or UTI. Some of these may not be evident during the initial examination, which should be frequently repeated. If the patient is still intubated and the chest X-ray does not reveal infiltrates, the possibility of tracheobronchitis or bacterial sinusitis should be considered. Staphylococci or enterobacteriaceae will cause most early infections. Grampositives predominate if quinolone prophylaxis is given.

Complications in the proximity of the surgical area must always be investigated. In OLT recipients, biliary anastomosis leaks may result in peritonitis or perihepatic collections. In heart and lung transplant recipients the possibility of mediastinitis (2-9%) should be considered. It may initially appear merely as fever or bacteremia of unknown origin. Inflammatory signs in the sternal wound, sternal dehiscence and purulent drainage may appear later (32). The most commonly involved microorganisms are staphylococci but gram-negative rods represent at least a third of our cases (30). Extensive surgical debridement and prolonged antimicrobial therapy are necessary. Herpetic stomatitis and infections transmitted with the allograft or present in the recipient may also appear at this time.

Bleeding or anastomosis dehiscences may require a new surgical intervention. Prolonged ICU stay due to CNS lesions or organ failure usually implies involvement of more resistant species such as VRE, *Acinetobacter*, *Pseudomonas*, MRSA or *Candida* (31). *Aspergillus* may also cause early infection in patients requiring prolonged admission to the ICU and who are especially difficult to diagnose (28).

From the second to the sixth month, patients are susceptible to opportunistic pathogens that take advantage of the immunosuppressive therapy. Most life-threatening infections occur within the first 3 months. Cytomegalovirus (CMV) is the most common pathogen after

SOT. When no prophylaxis is given, 30%-90% of patients will show laboratory data of "CMV infection" and 10-50% may develop associated clinical manifestations (CMV disease). However, CMV disease is readily diagnosed at present and seldom requires ICU admission. In our experience, only gastrointestinal and respiratory CMV has required ICU admission. Cultures for HHV-6 should be ordered in patients with leukopenia. Some bacterial infections such as listeriosis may appear at this time as primary sepsis or meningitis. Tuberculosis and nocardiosis are also characteristic of this second period (32).

Aspergillosis affects up to 5% of SOT and the risk is increased in patients with acute liver failure or renal insufficiency (33). Pulmonary involvement is described in 90% of the cases, but CNS or disseminated manifestations may predominate (34). The isolation of *Aspergillus* from any SOT recipient sample is always a warning clue.

The possibility of a *Toxoplasma* primary infection should be considered when a seronegative recipient receives an allograft from a seropositive donor. HT recipients are more susceptible to toxoplasmosis, which may be transmitted with the allograft and occasionally requires ICU admission. The risk of primary toxoplasmosis (R-D+) is over 50% in HT, 20% after liver transplantation and <1% after kidney transplantation. Patients with toxoplasmosis have fever, altered mental status, focal neurological signs, myalgias, myocarditis and lung infiltrates. Allograft-transmitted toxoplasmosis is more often associated with acute disease (61%) than with reactivation of latent infection (7%). Leishmaniasis is another parasitic infection that should be excluded, though it is exceedingly uncommon after SOT. It may present as fever, pancytopenia and splenomegaly.

From the sixth month onwards SOT patients are susceptible to community-acquired infections if chronic rejection is not present. Herpes zoster virus, bacterial pneumonia and UTI predominate. At this time, fever of unknown origin should be managed almost as in immunocompetent hosts. However, the aforementioned opportunistic infections may complicate this late period in patients with recurrent VHC or HBV, chronic hemodyalisis, malignancy or late rejection (35).

6. WHICH NON-INFECTIOUS CAUSES OF FEVER SHOULD BE EXCLUDED?

Both infectious and non-infectious causes of fever should be considered when approaching a febrile SOT patient. In a recent series, 87% of the febrile episodes detected in OLT in the ICU were infectious and 13% non-infectious (8). Rejection, malignancy, adrenal insufficiency and drug fever were the most common non-infectious causes.

Fever is common in the first 48 h after surgery and after certain procedures. If it is not persistent or accompanied by other signs or symptoms it should not trigger any diagnostic action. Acute rejection accounts for 4-17% of the non-infectious febrile episodes (29). It is usually related to an impairment of the allograft function and usually requires histological confirmation. It is more common in the first six months. Malignancy, mainly lymphoproliferative disease, is relatively common after SOT and may initially present as a febrile episode. It usually occurs longer after transplantation. (29). Acute adrenal insufficiency should be excluded in SOT patients admitted to an ICU because of sepsis or surgery, mainly when corticosteroids have been withdrawn and drugs that accelerate the degradation of cortisol (phenytoin, rifampin) are administered (36). However, although analytical adrenal insufficiency is frequent in SOT patients, prospective studies suggest that supplemental steroids are not needed in most cases even under stress (37-39). Another setting of potential adrenal insufficiency are renal transplants that return to dialysis (40, 41). Drugs such as OKT3, ATG, antimicrobials, interferon, anticonvulsants etc may also cause fever in this population. The temporal relationship with the drug is usually a diagnostic clue.

Other causes of non-infectious fever include thromboembolic disease, hematoma reabsortion, pericardial effusions and transfusion reaction. Non-cardiogenic pulmonary edema (pulmonary reimplantation response) is a common finding after lung transplantation (50-60%) and may occasionally lead to a differential diagnosis with pneumonia. It conditions prolonged mechanical ventilation and ICU stay but does not affect survival (42).

7. WHAT IS THE DIAGNOSTIC WORK-UP TO A FEBRILE SOT PATIENT WITH A SUSPECTED INFECTION?

The findings provided by the anamnesis and physical examination may suggest a focus causative of the fever (pneumonia, wound infection, etc). In this situation, a list of possible pathogens as well as necessary samples and tests for diagnosis should be elaborated. In most cases, analytical and imaging studies will also be ordered. Samples for culture should be obtained before starting empirical antimicrobial therapy.

In a recent study, 79% of the infections associated with fever in the liver recipients in the ICU were bacterial, 9% viral, and 9% fungal. Accordingly, blood cultures are practically always needed. Bacteremia is present in 45% of the febrile critical SOT patients and its origin must always be investigated. In liver recipients the most common sources are IV devices, lung, biliary tree and wound infections. Accordingly, the entry site of the catheters must be examined. MRSA and *P. aeruginosa* caused 65% of the bacteremias in ICU patients (7). Lack of febrile response in bacteremic OLT recipients portended a poorer outcome (43).

Pneumonia accounts for 30% of infections associated with fever in the ICU (41% of all febrile infections during the first 7 d of ICU stay and 14% of those after 7 d) (8). Singh has recently analyzed 40 OLT who developed lung infiltrates in the ICU (35). The etiology was: pulmonary edema 40%, pneumonia 38%, atelectasis 10%, ARDS 8%, contusion 3%, and unknown 3%. The signs that suggest an infectious origin were: Pugin score >6 (73% vs. 6%), abnormal temperature (73% vs 28%), and creatinine level >1.5 mg/dl (80% vs 50%) (35). MRSA, *P. aeruginosa* and Aspergillus caused 70% of all pneumonias in the ICU (8). All *Aspergillus* and 75% of MRSA pneumonias, but only 14% of the Gram-negative pneumonias occurred within 30 days of transplantation. *Legionella, T. gondii* and *CMV* may also cause pneumonia in this setting (7, 44). After HT, opportunistic microorganisms cause 60% of the pneumonias, nosocomial pathogens 25% and community-acquired bacteria and mycobacteria 15% (45). Once pneumonia is identified, respiratory samples and urine for *Legionella* and *S. pneumoniae* antigen detection must be sent to the lab (if possible, before starting antimicrobials). A bronchoscopic sample with bronchial biopsy is preferable for CMV, *Aspergillus* or *P. carinii* pneumonia. If pleural fluid is present it should also be analyzed.

If other clinical foci are present, appropriate samples must be sent to the laboratory (catheter tips, wound exudate, CSF, etc) as in any other critical patient. When a collection of fluid or pus is to be sampled, aspirated material provides more valuable information.

8. WHAT IS THE DIAGNOSTIC APPROACH TO A FEBRILE SOT PATIENT WITHOUT AN IDENTIFIABLE FOCUS OF FEVER OR INFECTION?

A major difference with immunocompetent critical patients is that the list of potential etiological agents is much longer and is influenced by time elapsed from transplantation. CMV (as main offender or as co-pathogen) should be considered in practically all-infectious complications in this population. Accordingly, a sample for CMV antigenemia (or PCR if available) should always be obtained. Other viruses such as adenovirus, influenza A or HHV-6 may also cause severe infections after SOT and can be recovered from respiratory samples or blood. If indicated, invasive diagnostic procedures should be performed rapidly and a serum sample stored.

Bacterial infections must always be considered and urine and blood cultures obtained before starting therapy. Diagnosis of catheter-related infections without removing the devices may be attempted in stable patients. Lysis centrifugation blood cultures as well and hub and skin cultures have a high negative predictive value (47). The first steps for diagnosis of pneumonia should include a chest X-ray and culture of expectorated sputum or bronchoaspirate (submitted for virus, bacteria, mycobacteria and fungus). A CT scan or ultrasonography may also be ordered to exclude the presence of collections in the proximity of the surgical area. Lumbar puncture and cranial CT (including the paranasal sinus) must be performed if neurological symptoms or signs are detected. In case of diarrhea, *C. difficile* should be investigated.

Tuberculosis is not common after SOT but the incidence is 20-25 times higher than in the general population (32, 46). A high index of suspicion is recommended. Fungal infections should be aggressively pursued in colonized patients and in patients with risk factors. Early stages of fungal infection may be very difficult to detect (34, 47). Isolation of *Candida* or *Aspergillus* from superficial sites may indicate infection. Fundi examination, blood and respiratory cultures and *Aspergillus* and *Cryptococcus* antigen detection tests must be performed.

Parasitic infections are uncommon, but toxoplasmosis and leishmaniasis should be considered if diagnosis remains elusive. Serology or bone marrow cultures usually provide the diagnosis.

9. WHAT READILY AVAILABLE MICROBIOLOGICAL INFORMATION SHOULD BE SOUGHT?

Information on some of the most severe infections may be obtained rapidly when the clinician and the microbiology laboratory communicate effectively and the best specimen type and test are selected.

Antigen detection tests for adenovirus, HSV, Influenza A, RSV, rotavirus etc. are available. Most common herpesviruses can be easily cultured and detected.

Gram stain requires expertise but may provide valuable rapid information (5 minutes) on the quality of the specimen and whether gram-negative or positive rods or cocci are present. It may reveal yeast and occasionally molds, parasites, *Nocardia* and even mycobacteria. The amount of material and the number of organisms limit detection sensitivity.

Continuous agitation blood cultures have significantly reduced the detection time to less than 24 hours for bacterial isolates.

Direct testing of specimens with antigen assays are mainly used for CSF samples (*N. meningitidis, S. pneumoniae, C. neoformans*). Group A streptococci, *Clostridium difficile* and *C. trachomatis* antigen detection tests are also available. Specific stains for *Legionella* (DFA) and *B. pertussis* are offered by most laboratories. *Legionella* urinary antigen test will be very useful in pneumonias caused by *L. pneumophila* serotype 1 and *S. pneumoniae* antigenuria can also be rapidly investigated. HIV infection, *Brucella* or syphilis are some of the infections that can be rapidly diagnosed serologically.

Acid-fast stain and fluorochrome stains for mycobacteria or *Nocardia* require a more prolonged laboratory procedure (30-60 minutes). *M. tuberculosis* complex PCR is very effective in smear-positive specimens. In smear-negative samples sensitivity is ~ 70%.

Fungal elements may be rapidly detected in wet mounts with potassium hydroxide or immunofluorescent Calcofluor white stain. An India ink preparation allows the identification of encapsulated *C. neoformans*, particularly in CSF in approximately 50% of patients. The latex agglutination test or EIA cryptococcal antigen have greater sensitivity. Fluorescent antibody stains or toluidine blue O permit the detection of *P. carinii.* Antigen detection for *H. capsulatum* is quite sensitive and the detection of *Aspergillus* antigen is a promising technique.

10. WHAT IS THE OUTCOME OF FEBRILE PROCESSES OF SOLID ORGAN TRANSPLANT RECIPIENTS IN THE ICU?

SOT patients have higher risk of dying after an ICU admission than the general population. However, the overall prognosis is better than that of bone marrow recipients (48-50). The overall ICU mortality of SOT patients was 18% in a recent series and infection was the major cause of death (disseminated mycoses, HCV, multiorganic failure, hepatic artery thrombosis with sepsis and primary nonfunction of the graft (1).

Mortality of febrile liver recipients at 14 d (24 versus 0%, p = 0.001) and at 30 d (34 versus 5%, p = 0. 001) was significantly higher in the ICU, as compared to non-ICU patients (8). Mortality of OLT with lung infiltrates in the ICU was 28%. Pneumonia, creatinine level >1.5 mg/dl, higher blood urea nitrogen, and worse APACHE neurological score were predictors of poor outcome. (35). The need for mechanical ventilation was an independently significant predictor of mortality. (7).

Infection is also a leading cause of death in heart recipients (30% of early deaths, 45% of deaths from 1 to 3 m and 9.7% thereafter) (51). Overall, 31% of the patients with pneumonia died (*Aspergillus* 62%; CMV 13% ; nosocomial bacteria 26%). Mortality was 100% in patients requiring mechanical ventilation (7/13 *Aspergillus*, 5/11 *P.carinii*, 1/8 CMV) (45).

Mortality of renal transplant recipients in the ICU was 11% in a recent series and infection caused 6/7 deaths (9).

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