Opportunistic Fungal and Bacterial Infection in the Renal Transplant Recipient

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(J. Am. Soc. Nephrol. 1992; 2:S264–S269)

ABSTRACT
The risk of opportunistic infection in the renal transplant recipient is determined by the interaction between two factors: the epidemiologic exposures the individual encounters within the community and the hospital and a complex function termed the net state of immunosuppression. There are two general categories of opportunistic fungal infection in this patient population: (1) disseminated primary or reactivation infection with one of the geographically restricted systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis) and (2) opportunistic infection with fungal species that rarely cause invasive infection in the normal host (Aspergillus species, Candida species, Cryptococcus neoformans, and the Mucoraceae), with these last usually being acquired within the hospital environment. Newly available azole compounds, fluconazole and itraconazole, are exciting new alternatives to amphotericin in the treatment of at least some of these infections. The three most important forms of opportunistic bacterial infections are those due to Listeria monocytogenes, Nocardia asteroides, and a variety of mycobacterial species. Clinical diseases with these first two are effectively prevented by low-dose trimethoprim-sulfamethoxazole prophylaxis. There are two cardinal therapeutic rules to be followed by clinicians in dealing with these infections: prevention is better than treatment; when treatment is required, however, the major determinant of the success of therapy is the rapidity with which the diagnosis is made and effective therapy is initiated.

Key Words: Fungal infection, bacterial infection, renal transplant

Opportunistic infection, as it occurs in the renal transplant recipient, may be categorized as fitting into one of the following two categories: (1) tissue invasive disease due to microorganisms that are often ubiquitous in the environment and that are incapable of causing more than mucocutaneous colonization in the normal host; and (2) disseminated infection of a type and severity unknown in the normal host, although the microbe in question may produce localized or self-limited disease in the individual whose natural immunity and specific immune responses are intact. Examples of the first category include invasive aspergillosis, Pneumocystis carinii pneumonia, and cryptococcal meningitis; examples of the second category include disseminated histoplasmosis, disseminated candidiasis, and disseminated mycobacterial infection (1–3). The purpose of this review is to discuss the epidemiology, clinical presentation, and management of opportunistic infection in the renal transplant patient, concentrating particularly on the fungal and bacterial pathogens that are the major causes of such infection.

The risk of opportunistic infection in the renal transplant recipient is determined by the interaction of two factors, the epidemiologic exposures the individual encounters and the individual’s net state of immunosuppression (1,4). As outlined in Table 1, the epidemiologic exposures can be divided into two general categories: those encountered in the community and those encountered within the hospital. Within the community, both recent and remote exposures to such organisms as the geographically restricted systemic mycoses (Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitidis), typical and atypical mycobacterial species, the parasite Strongyloides stercoralis, and the human immunodeficiency virus are of particular importance.

Exposures of importance within the hospital environment can be divided into two categories as well, domiciliary and nondomiciliary. Domiciliary exposures occur when aerosols laden with microorganisms such as Aspergillus and Legionella species and gram-negative bacteria such as Pseudomonas aeruginosa are blown onto the wards where patients
TABLE 1. Epidemiologic exposures of particular importance in the renal transplant patient in the pathogenesis of opportunistic infection

<table>
<thead>
<tr>
<th>Community Based</th>
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<tr>
<td>Geographically restricted systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis)</td>
</tr>
<tr>
<td>Mycobacterial infection*</td>
</tr>
<tr>
<td>S. stercorali</td>
</tr>
<tr>
<td>Hospital Based</td>
</tr>
<tr>
<td>Aspergillus species</td>
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<tr>
<td>Legionella species</td>
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<tr>
<td>Other gram-negative bacteria, particularly P. aeruginosa</td>
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* Although not usually considered opportunistic infections, the severity, attack rates, and clinical consequences of these infections in renal transplant patients argue for their inclusion in this table.

are housed. The epidemics that ensue are identified relatively easily because of the clustering of cases in time and space; such epidemics are relatively easily prevented by the provision of HEPA filtered air to these patients’ rooms. Nondomiciliary exposures occur when the infection-laden aerosols are encountered at central sites within the hospital to which patients are taken for essential procedures. Such central sites include the radiology suite, the operating room, and the cardiac catheterization laboratory. Unfortunately, such exposures are less easy to discover because of the lack of clustering of cases on a given ward and are far more difficult to prevent. The clinician responsible for the infectious disease management of transplant patients must maintain an active surveillance for such infections, paying particular attention to construction activities within the hospital because these typically liberate large amounts of microorganisms into the air. Transplant patients must be protected from such exposures (5,6).

The net state of immunosuppression is a complex function, (Table 2) driven largely by the dose, duration, and temporal sequence in which immunosuppressive therapy is deployed, but is also magnified by the other factors listed. Of particular importance is the effect of the immunosuppressive therapy on the occurrence of infection with the immunomodulating viruses, cytomegalovirus (CMV), Epstein-Barr virus, the hepatitises, and the human immunodeficiency virus. Thus, not only does the immunosuppressive therapy prescribed contribute directly to the net state of immunosuppression, but by activating and promoting infection with these viruses, the immunosuppressing effect is greatly amplified. For example, at our hospital, more than 90% of opportunistic infections that have occurred among renal transplant patients over the past decade have occurred as superinfection in individuals with immunomodulating viral infection. Indeed, the exceptions

<table>
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<tr>
<th>TABLE 2. Factors contributing to the net state of immunosuppression in the renal transplant recipient</th>
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<tr>
<td>Dose, duration, and temporal sequence in which immunosuppressive agents are administered</td>
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<tr>
<td>The presence of granulocytopenia, injury to the mucocutaneous surfaces of the body</td>
</tr>
<tr>
<td>Such metabolic factors as malnutrition, uremia, and, perhaps, hyperglycemia</td>
</tr>
<tr>
<td>The presence of immunomodulating viral infection due to CMV, Epstein-Barr virus, the human immunodeficiency virus, and/or the hepatitis viruses</td>
</tr>
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represented instances of unusually intense nosocomial epidemiologic hazards (1–4).

PRINCIPLES OF CLINICAL MANAGEMENT OF OPPORTUNISTIC INFECTION IN THE RENAL TRANSPLANT PATIENT

The following principles represent both the important themes of clinical practice in these patients and the challenges that face the clinician who must accomplish these tasks. (1) Prevention of infection is the primary goal. Therefore, the attention of the clinician should be directed not only to the recognition and treatment of opportunistic infection but also to the identification and correction of possible epidemiologic hazards as well as the attempt to protect the patient during periods in which the net state of immunosuppression is at its greatest. Practically, this last issue is best approached by preventative programs of antimicrobial therapy, particularly those aimed at the immunomodulating viruses such as CMV. The point to be emphasized is that the therapeutic prescription for the transplant patient includes two components: the immunosuppressive therapy that prevents the allograft from being rejected and the antimicrobial strategy that makes such immunosuppressive therapy safe (1–4).

(2) There are three different modes in which antimicrobial therapy may be prescribed to the renal transplant patient (7).

(A) Prophylactic antimicrobial therapy involves the administration of an antimicrobial agent before an event (such as surgery) to a large population of patients in order to prevent infection. In order to justify such prophylactic therapy, two requirements must be met: the treatment should be nontoxic and the infection should be common enough or important enough to justify the administration of such therapy to large numbers of individuals. Low-dose trimethoprimsulfamethoxazole (80 mg of trimethoprim and 400 mg of sulfamethoxazole at bedtime) is an important example of such prophylaxis because it markedly decreases the incidence of urinary tract infec-
tion, while preventing such opportunistic infections as those due to *P. carinii*, *Nocardia asteroides*, and *Listeria monocytogenes* (1).

(B) Therapeutic antimicrobial therapy is the traditional manner in which antimicrobial therapy is prescribed and consists of the administration of curative treatment to patients with established infection.

(C) Preemptive antimicrobial therapy consists of the administration of an antimicrobial agent before clinical evidence of infection, on the basis of careful clinical epidemiologic assessment and/or laboratory evaluation. For example, the administration of low-dose ganciclovir therapy (2.5 mg/kg/day) in association with antilymphocyte antibody therapy markedly decreases the incidence of symptomatic CMV disease; the administration of fluconazole to renal transplant patients with asymptomatic candiduria decreases the incidence of candidal pyelonephritis, obstructing fungal balls, and disseminated infection (7,8).

(3) The clinical presentation of opportunistic infection in the transplant patient is usually occult, with the extent of disease at the time of diagnosis often far out of proportion to the severity of the symptoms. This is due to two factors: the majority of the organisms causing such infections are relatively bland, exciting little in the way of inflammatory signs or symptoms; and, even more important, the patient's immunosuppressed state will limit his or her ability to mount an inflammatory response, again decreasing the signs and symptoms present. Because the success of therapy is directly related to the rapidity with which a diagnosis is made and specific treatment initiated, the diagnostic acumen of the responsible clinician is constantly being challenged to achieve early diagnosis. For this reason, invasive biopsy techniques are employed expeditiously in the evaluation of even bland-appearing skin and pulmonary lesions in this patient population (1).

(4) Therapy for most of these infections is rendered particularly difficult by the toxicity of most of the available therapies and the usual requirement for a prolonged course of treatment. This problem has become particularly important in the present era of cyclosporine-based immunosuppression. A broad array of antimicrobial agent-cyclosporine interactions must be kept in mind, because not only will certain antimicrobial agents affect cyclosporine pharmacokinetics, but many antimicrobial agents will interact with cyclosporine to produce nephrotoxicity that is far more severe than that produced by either drug by itself (Table 3).

FUNGAL INFECTIONS OF IMPORTANCE IN THE RENAL TRANSPLANT PATIENT

There are two general categories of opportunistic fungal infection that occur in transplant patients:

<table>
<thead>
<tr>
<th>TABLE 3. Drug interactions occurring between cyclosporine and commonly used antimicrobial agents</th>
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<tbody>
<tr>
<td>Up-regulation of hepatic cytochrome P450 function, resulting in increased cyclosporine metabolism, lower blood levels, and an increased incidence of rejectiona</td>
</tr>
<tr>
<td>Example: rifampin</td>
</tr>
<tr>
<td>Inhibition and/or down-regulation of hepatic cytochrome P450 function, resulting in decreased cyclosporine metabolism, higher blood levels, cyclosporine toxicity, and increased immunosuppressionb</td>
</tr>
<tr>
<td>Examples: erythromycin, ketoconazole, itraconazole, fluconazole</td>
</tr>
<tr>
<td>Unexplained interaction with cyclosporine to produce synergistic nephrotoxicityb</td>
</tr>
<tr>
<td>Examples: amphotericin, aminoglycosides, high-dose trimethoprim-sulfamethoxazole, vancomycin</td>
</tr>
</tbody>
</table>

a Both of these types of interaction may be monitored by serial measurements of cyclosporine blood levels, and, when necessary, appropriate adjustment to cyclosporine dosage may be made.

b Serial measurements of cyclosporine blood levels have not been of value in the prevention of this form of drug interaction.

disseminated primary and reactivation infection (in addition, reinfection may occur in a small number of patients whose immunity has been blunted by immunosuppressive therapy) with one of the geographically restricted systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidiomycosis); and opportunistic infection with fungal species that rarely cause invasive infection in the normal host (Aspergillus species, *Candida* species, *Cryptococcus neoformans*, and the *Mucoraceae*). In the first category of infection, there are several clinical presentations that should suggest the occurrence of one of these infections (or disseminated mycobacterial infection) in individuals who have been exposed to the appropriate geographic areas: a subacute respiratory illness, with either focal or disseminated interstitial or miliary infiltrates on chest X-ray; a nonspecific febrile illness (a "fever of unknown origin") of more than 5 days' duration; or an illness in which metastatic aspects of the infection predominate (e.g., mucocutaneous manifestations in histoplasmosis and blastomycosis or central nervous system manifestations in coccidioidomycosis). Systemic mycoses of this type in the renal transplant patient differ from such infections in two important ways (characteristics typical of opportunistic pathogens)—disseminated infection is the rule and should be assumed, and even localized infection in this patient population always requires antifungal chemotherapy (1–3).

The more common problem is the acquisition of invasive fungal infection with one of the normally saprophytic organisms that are ubiquitous in the general environment. Nosocomial acquisition is the rule with these organisms, particularly during pe-
Transplant period of construction and remodeling, when aerosols of such organisms can be created, resulting in life-threatening invasive disease even in individuals whose net state of immunosuppression would not normally be great enough for such infections to occur. Two clinical patterns of infection are observed with these normally saprophytic organisms in the transplant patient: primary infection, usually of the lungs, occasionally of the nasal sinuses, caused most commonly by *C. neoformans, Aspergillus* species, or, less commonly, the *Mucoraceae*; and sequential or concomitant secondary infection, either of lungs or mucocutaneous surfaces previously damaged by other processes or via infected i.v. lines, with *Candida* species, *Aspergillus* species, *Torulopsis glabrata*, and the *Mucoraceae*. In the case of the *Mucoraceae*, two metabolic factors have recently been defined that increase the patient's susceptibility to invasive infection with this group of opportunistic fungi. The first of these has to do with the role of acidosis in the promotion of this infection. Rhinocerebral mucormycosis has long been recognized as an important complication of diabetic ketoacidosis, with elegant experimental studies demonstrating that the acidosis rather than the hyperglycemia plays an important role in the pathogenesis of these infections (9). With the advent of combined pancreatic-renal transplantation for diabetics, in which the pancreatic duct is connected to the bladder so that all pancreatic exocrine secretion is voided, the importance of acidosis has been reemphasized. Whereas invasive mucormycosis is a highly unusual opportunistic infection in renal transplant patients, patients with combined pancreatic and renal transplants with moderate amounts of renal dysfunction develop acidosis because of the continuing bicarbonate leak that cannot be corrected by the ailing kidney, resulting in systemic acidosis in the face of euglycemia; in such a setting, invasive pulmonary and rhinocerebral mucormycosis has occurred. Thus, the replacement of bicarbonate in these individuals is important from an infectious disease as well as a metabolic point of view. The second metabolic factor that can predispose to mucormycosis that is relevant to the renal transplant population is the use of deferoxamine in patients on dialysis (10).

With all forms of fungal infection in the transplant patient, it is important to emphasize that it is not enough just to identify the primary site of infection. As with malignant disease, a careful search for sites of metastatic infection, particularly within the central nervous system (CNS), skin, and skeletal system, should be undertaken. On the one hand, the prognosis is largely determined by whether or not metastatic spread has occurred (for example, at our institution the survival rate for invasive pulmonary aspergillosis is approximately 85% if no metastases can be demonstrated at the initiation of therapy, and <5% if CNS metastases have occurred); on the other hand, treatment must be designed to cure both primary and metastatic sites.

Treatment of invasive fungal infection in the transplant patient is greatly complicated by the fact that the administration of amphotericin in the face of cyclosporine-based immunosuppression is associated with an accelerated rate of severe nephrotoxicity. Despite this, amphotericin B remains the cornerstone of therapy for invasive aspergillosis or mucormycosis, perhaps with "wrap-up" therapy with the experimental compound itraconazole (11). In the case of *C. albicans, Candida tropicalis*, and *C. neoformans* infection, fluconazole has proven to be a useful alternative to amphotericin provided the following points are kept in mind. (1) When amphotericin therapy has been compared with fluconazole directly in randomized trials, although the overall results are similar, amphotericin "gains control of the disease process" more rapidly than fluconazole (13). Therefore, for rapidly evolving acute disease, we initiate therapy with amphotericin, despite toxicity issues, until the patient stabilizes and then switch to fluconazole. For patients with more subacute presentations, primary therapy with fluconazole in transplant patients with these infections has been quite successful. (2) Fluconazole does affect the pharmacokinetics of cyclosporine, inhibiting the hepatic metabolism of the drug, thus resulting in higher blood levels and mild degrees of cyclosporine nephrotoxicity. This is easily managed in the majority of patients by monitoring renal function and cyclosporine blood levels and making small reductions in the cyclosporine and/or fluconazole dose (12,13). (3) There are other strains of yeast, particularly *Candida krusei*, that are relatively resistant to fluconazole, and other therapies must be employed, primarily amphotericin (14). (4) As far as the systemic mycoses (histoplasmosis, coccidiomycosis, and blastomycosis) are concerned, amphotericin remains the treatment of choice, although preliminary experience with fluconazole and itraconazole appears to be promising (11).

**OPPORTUNISTIC BACTERIAL INFECTIONS OF IMPORTANCE IN THE TRANSPLANT PATIENT**

There are three forms of bacterial infection that can be classified as opportunistic that occur in the renal transplant patient: infection due to *L. monocytogenes*, infection due to *N. asteroides*, and mycobacterial infection. Although all three of these types of infection can occur in the normal individual, the incidence, degree of dissemination, and severity of illness are far higher in immunocompromised patients such as the renal transplant recipient.

*L. monocytogenes* is a gram-negative bacillus
whoose portal of entry is the gastrointestinal tract after the ingestion of contaminated foods. The clinical syndromes resulting from such an event are as follows: bacteremia, sometimes in the setting of a gastroenteritis syndrome; an acute-subacute meningitis (on the one hand, meningitis is the most common clinical syndrome observed with this organism in transplant patients; on the other hand, L. monocytogenes is the most common cause of pyogenic meningitis in transplant patients); meningococcemia; and cerebritis without concomitant meningitis. Therapeutically, two points bear emphasis: low-dose trimethoprim-sulfamethoxazole prophylaxis, as previously described, effectively prevents Listeria infection in transplant patients; this organism has a particular tropism for the CNS such that seeding of the CNS should be assumed in any patient with bacteremia, even if a lumbar puncture is negative. Thus, meningococcal doses of antibiotics are prescribed routinely: high-dose penicillin or ampicillin (plus or minus systemic gentamicin for synergistic killing of the organism), with high-dose trimethoprim-sulfamethoxazole as an alternative in the penicillin-allergic individual (1,15).

N. asteroides, although commonly grouped with fungal infections because of a common pathogenesis and clinical presentation, is not an uncommon cause of life-threatening infection in transplant patients not receiving trimethoprim-sulfamethoxazole prophylaxis. In such individuals, the typical presenting complaint is of cough and fever, with one or more focal (usually nodular) infiltrates abutting the pleura on chest X-ray. Again, like the fungal infections that begin in the lung (and also like tuberculosis), early blood vessel invasion and hematogenous dissemination to the skin, CNS, and the skeletal system are common events. Indeed, metastatic lesions, particularly of the skin or CNS, may be the first recognizable sign of disseminated nocardial infection. Prolonged therapy (at least 4 to 6 months) with sulfasoxazole or trimethoprim-sulfamethoxazole is the standard of care, with such drugs as minocycline, imipenem, and amikacin being used primarily in patients with life-threatening drug allergies (1,16).

Mycobacterial infection in the transplant patient must be considered in two categories: (1) typical Mycobacterium tuberculosis infection, which is not truly opportunistic, although the incidence of extrapulmonary and miliary tuberculosis is much higher in this patient population than among nonimmunosuppressed individuals; (2) atypical mycobacterial infection, particularly of the skin, which is opportunistic in nature, occurring predominantly at skin sites previously damaged by other processes, particularly water immersion injury. Such organisms as M. marinum, M. cheloni, M. haemophilum, and other species have been recognized among transplant recipients (1-4).

OTHER FORMS OF OPPORTUNISTIC INFECTION OF IMPORTANCE IN THE TRANSPLANT PATIENT

The incidence of P. carinii pneumonia (extrapulmonary Pneumocystis infection akin to that seen in AIDS patients is essentially unknown in this patient population) among transplant patients not receiving trimethoprim-sulfamethoxazole prophylaxis has been reported as 5 to 10%. Such infections are thought to represent the reactivation of latent infection acquired early in life. Although previously classed as a protozoan, the genus Pneumocystis is now classified as a fungus, albeit one that responds clinically to drugs with activity against protozoan organisms as opposed to antifungal drugs. In the transplant patient, P. carinii infection is closely linked to the presence of coinfection with cytomegalovirus, possibly because of the key role of alveolar macrophages in the host defense against Pneumocystis infection, as well as the marked suppression of alveolar macrophage function induced by CMV. The usual clinical presentation is subacute, with fever, nonproductive cough, and progressive dyspnea being the cardinal manifestations. Radiologic manifestations are typically those of a bilateral, relatively symmetrical interstitial pneumonia, predominantly of the lower lobes. Atypical appearances include a lobar consolidation and an isolated nodule. Diagnosis is made in the majority of patients by bronchoalveolar lavage, although, on occasion, lung biopsy may be necessary. Therapy with high-dose trimethoprim-sulfamethoxazole (20 mg of trimethoprim and 100 mg of sulfamethoxazole/kg/day) or pentamidine (5 mg/kg) in association with a 5- to 7-day course of increased steroid administration is quite effective in treating Pneumocystis infection in this patient population. However, because of the high rate of side effects with these regimens (particularly nephrotoxicity) in cyclosporine recipients, emphasis is placed on prevention with the two-dose prophylaxis regimen during periods of greatest risk: first 6 months posttransplant and in patients with chronic graft dysfunction and chronic viral infection (1).

The one true protozoan opportunistic infection that can have a major effect on transplant patients is that due to S. stercoralis. This organism is unique among intestinal nematodes in two ways: (1) because of its ability to perpetuate itself with an autoinfection cycle, it can persist in the gastrointestinal tract of individuals many years after exposure; and (2) the initiation of immunosuppressive therapy can result in the amplification of this infection, with tissue invasion and dissemination. The result can be two life-threatening clinical syndromes in the compromised host: a hyperinfection syndrome, which is an exaggeration of the normal life cycle of the parasite, with a major effect on the gastrointestinal tract (a severe hemorrhagic enterocolitis) and lungs (hemor-
rhagic pneumonia); and a disseminated strongylo-
idiasis syndrome, in which the worms, often accom-panied by gram-negative bacteria from the gut, can invade the abdominal viscera, CNS, lungs, and other tissues. The presenting clinical events recognized in this latter form of Strongyloides infection include unresponsive gram-negative bacteremia or meningitis. Although patients with the fully developed syndrome can occasionally be salvaged with repeated courses of oral thiabendazole and antibacterial agents, it is far better to eradicate the carriage of these organisms before transplantation in individuals with a history of even remote exposures to areas of the world endemic for this infection (tropical and developing countries) (1).

Although Toxoplasma gondii is an important pathogen in heart transplant patients and AIDS pa-tients, it is a rare cause of clinical disease in the renal transplant recipient. Unlike cardiac muscle, renal tissue rarely harbors this organism and, hence, disseminated primary infection of donor origin is quite rare. Because the net state of immunosuppression in renal transplant patients is far less than that in AIDS patients, the reactivation and dissemination of toxo-plasmosis throughout the brain and other sites is likewise a rare event in renal allograft recipients (1).

SUMMARY

Despite the success of renal transplantation, oppor-tunistic infection, particularly that caused by cer-tain fungi and bacteria, continues to be a clinical problem. The risk of opportunistic infection is deter-mined by the interaction between two major factors: the epidemiologic exposures the patient encounters and the net state of immunosuppression. The goal of the clinician is the prevention of opportunistic infection by the following means: identifying and protect-ing the patient from excessive environmental haz-ards, particularly within the hospital environment; and the use of antimicrobial agents either prophylactically or preemptively in order to protect against the infection-promoting effects of the necessary immuno-suppressive therapy. When, despite these efforts, infection does develop, disseminated infection in the face of a minimum of clinical signs and symptoms is the general pattern, requiring alertness and aggres-siveness on the part of the clinician in the evaluation of even minor abnormalities. Success in the treat-ment of opportunistic infection in the renal trans-plant recipient is directly related to the speed with which diagnosis is made and specific therapy initi-ated.

REFERENCES