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Mycophenolate Mofetil and its Immunological Footprint: A Comprehensive Review of Infection Risk in Transplant and Autoimmune Patients

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A B S T R A C T :

Mycophenolate mofetil (MMF) stands as a pivotal immunosuppressive agent, widely utilized in solid organ transplantation to prevent allograft rejection and in the management of various autoimmune diseases. Its mechanism of action, centered on the inhibition of inosine monophosphate dehydrogenase (IMPDH), Selectively Suppresses lymphocyte proliferation. While undeniably effective in controlling Immune responses, this potent immunosuppression significantly elevates a patient's susceptibility to a broad spectrum of infections. This comprehensive review synthesizes current evidence on the prevalence, diverse types, and key risk factors Associated with MMF-induced infections. We delve into the specific immunological Mechanisms that underpin this vulnerability, exploring impacts on both adaptive and Innate immunity. Particular attention is given to common and opportunistic viral (e.g.,Cytomegalovirus, BK polyomavirus, herpes zoster, Progressive Multifocal Leukoencephalopathy), bacterial (e.g., urinary tract infections, sepsis, Nocardia), and Fungal (e.g., Cryptococcus, Aspergillus) infections. Furthermore, we explore critical Patient-specific and treatment-related risk factors, alongside Acurrent monitoring and Management strategies, including the role of prophylaxis and dose adjustments. Finally, we highlight existing knowledge gaps and propose future research directions Aimed at optimizing therapeutic outcomes while mitigating infectious complications in MMF-treated individuals.

Keywords: Infection , Organ transplant, immunosuppression, autoimmune Disease

Introduction:

A condition known as immunosuppression is defined as a temporary or permanent immune system insufficiency brought on by shocks to the immune response that result in an enhanced immune system and disease resistance. [1]

Immunosuppressant drugs are essential pharmacological agents used to suppress or modulate the immune system's activity. They are essential for managing inflammatory disorders, reducing organ rejection after transplantation, and treating autoimmune diseases. For efficient illness management and better patient outcomes, it is essential to comprehend the mechanisms of immunological diseases, their underlying causes, and the function of immunosuppressants. A broad class of pharmaceutical substances known as immunosuppressant medications is intended to alter the activity of the immune system. Their main function is to reduce or attenuate immunological responses, which can help manage a variety of illnesses marked by abnormal immune activity. These ailments include organ transplantation, which stops the recipient's immune system from rejecting donor organs, and autoimmune illnesses, in which the body's own tissues are mistakenly attacked by the immune system. [2]

Table 1 Commonly used immunosuppressant drugs in organ transplant

ISDs	Class	Indication
Prednisone	Corticosteroids	Immunosuppression rejection, cellular rejection treatment
Cyclosporine	Calcineurin inhibiter	Immunosuppression maintenance

Tacrolimus	Calcineurin inhibiter	Immunosuppression maintenance
Sirolimus	Mammalian target of rapamycin inhibiter	Malignancies, rejection treatment, immunosuppression maintenance
Mycophenolate mofetil	Anti-metabolite	Rejection treatment, Immunosuppression maintenance

ISDs, Immunosuppressant drugs

The goal of anti-rejection therapy has changed from preventing acute transplant rejection to achieving adequate immunosuppression with low toxicity as a result of the development of novel immunosuppressive drugs. For nearly a decade, mycophenolate mofetil (MMF) has been used in kidney and pancreatic transplants. [3]

MMF is a recently developed immunosuppressive drug, which acts to inhibit T and B cell proliferation by blocking the production of guanosine nucleotides required for DNA synthesis. It also prevents the glycosylation of adhesion molecules that are involved in attachment of lymphocytes to endothelium and potentially in leukocyte infiltration of an allograft during an immune response. Reputable randomized clinical trials have shown that MMF, in combination with cyclosporine (CsA) and steroids, improves renal allograft survival at three years, decreases the frequency and intensity of acute rejection episodes in kidney and heart transplant recipients, and increases patient and graft survival in recipients of heart allografts. Additionally, it has been successful in treating acute and persistent rejection events in recipients of liver, kidney, and heart transplants. MMF's potential to help spare other immunosuppressive drugs is also encouraging, especially in cases of CsA-related nephrotoxicity. In individuals with chronic allograft nephropathy or CsA-related nephrotoxicity, MMF may stabilize or enhance renal graft function by allowing a decrease in CsA dosages. The two primary side effects of oral or intravenous MMF are hematologic and gastrointestinal. [4]

Pharmacological Profile of Mycophenolate Mofetil:

Mycophenolic acid (MPA), a fungal molecule, is a prodrug of MMF, a new immunosuppressant, which is made to increase its oral bioavailability. It is a medication used to treat refractory rejection following kidney transplantation. Because IMP dehydrogenase (IMPDH) is the rate-limiting enzyme in the de novo synthesis of GTP, MPA selectively, reversibly, and uncompetitively inhibits the generation of GMP (IC 50 = 25 nM). Therefore, MPA administration has immunosuppressive effects, including suppression of cytotoxic T cell production and antibody production, by selectively inhibiting the proliferation and activation of T and B lymphocytes, which rely primarily on the de novo pathway for guanidine nucleotide supply. However, MPA appears to have a selective effect on lymphocyte proliferation because it does not inhibit the expression of the IL-2 receptor. MPA decreased acute rejection in a canine renal allograft model, and it was shown that transplanted kidneys might survive over the long term. Furthermore, the administration of MMF and cyclosporine A (CsA) together suppressed the onset of rejection in a dog model of experimental GVHD, and the transplanted organ survived for a long time after the administration was stopped. This suggests that immune tolerance may be induced. Furthermore, kidney transplant clinical trials carried out in Japan and abroad have demonstrated that MMF suppresses the start of rejection and allows transplanted kidneys to survive for a long time. [5]

Mechanism of Action:

Mycophenolate mofetil is a 2-morpholinoethyl ester that is semisynthetic. It is a prodrug that plasma esterase quickly transforms into the active metabolite, MPA, in vivo. Inosine monophosphate dehydrogenase (IMPDH), a crucial enzyme in the de novo purine biosynthesis pathway, is selectively, uncompetitively, and reversibly inhibited by MPA, a strong immunosuppressive drug. An essential substrate for the synthesis of DNA and RNA, guanosine monophosphate is produced when inosine monophosphate (IMP) and xanthine monophosphate (XMP) are converted by the enzyme IMPDH. [6-7]

Type I and Type II are the two isoforms of IMPDH. Nonreplicating cells use the IMPDH type I isoform, whereas proliferating lymphocytes mostly use the IMPDH type II isoform. Because MPA binds to the IMPDH type II isoform five times more strongly, it depletes guanosine nucleotides, inhibits DNA synthesis, and stops replicating cells in the S phase. MMF is therefore more cytotoxic to T and B cells that are multiplying. [8]

While other cell types can use the salvage process, or hypoxanthine-guanine phosphoribosyl transferase pathway, T and B lymphocytes rely on the de novo production of purines for their proliferation. [9]

As a result, MPA has stronger cytostatic effects on T and B cells, lowers immunoglobulin levels, and delays type hypersensitivity reactions. [10]

Additionally, MMF inhibits the glycosylation of monocyte and lymphocyte glycoproteins involved in endothelial cell attachment. As a result, it causes immunological tolerance, hinders antigen presentation, and decreases chemotaxis. [11]

Pharmacology:

Pharmacokinetics:

Enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF) are the two forms of mycophenolic acid (MPA). A prodrug called MMF was created to increase MPA's bioavailability. By postponing the release of MPA into the small intestine rather than the stomach, EC-MPS may lower the frequency of unfavorable gastrointestinal (GI) effects, primarily diarrhea. The active metabolite MPA is quickly hydrolyzed from both formulations. [12]

Both formulations have a 90% bioavailability, although this is greatly decreased when taken with a high-fat diet. Therefore, in order to maximize absorption, both formulations should be taken empty-handed. The MMF formulation may also be taken with meals at regular intervals throughout the

day to enhance GI tolerance. [13]

1000 mg of MMF is therapeutically comparable to 720 mg of EC-MPS . Nevertheless, because the pace and degree of absorption of these two medications are not comparable, the two formulations should not be used interchangeably. To increase GI tolerance in certain individuals, switching from MMF (CellCept) to EC-MPS (Myfortic) is required. When this happens, further clinical effect monitoring is necessary. [14-15]

Dosages:

MMF is offered in the following forms: 250 mg capsules, 500 mg tablets, and an oral suspension powder (200 mg/ml). The equivalent of 500 mg MMF as the hydrochloride salt for intravenous administration is contained in a vial of lyophilized, sterile powder. Adults typically take 1.25 to 2 g of MMF per day. When skin conditions improve, the dosage can be lowered to 1 g per day in divided doses. It is given to children in doses of 600 mg/m every 12 hours, with a daily limit of 2 g. Patients with significant renal impairment may benefit from a dose reduction. [16, 17]

The delayed-release tablets of enteric-coated mycophenolate sodium (ECMS) come in 180 or 360 mg MPA concentrations. For patients who experience negative gastrointestinal symptoms from MMF, it can be used as a substitute. [18]

Clinical Applications:

An immunosuppressive medication called mycophenolate mofetil (MMF) inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH). In the de novo purine production of lymphocytes, IMPDH is a crucial enzyme. The proliferative responses of human T and B lymphocytes depend on it. Therefore, selective suppression of lymphocytes results from IMPDH inhibition. Following its effective application in a number of in vitro and animal models, MMF was introduced to clinical trials in transplant recipients. When used orally, the medication is quickly and fully absorbed. According to pilot studies, administering 1 to 3 g/day of cyclosporin with corticosteroids significantly decreased the risk of organ rejection. These investigations resulted in the creation of three pivotal randomised double-blind multicentre trials with a total of around 1500 patients to examine the impact of adding MMF to various standard immunosuppressive regimes on preventing acute renal allograft rejection. Patients receiving MMF experienced a significant decrease in biopsy-proven rejection rates at six months. When cyclosporin and corticosteroids were combined, the adverse impact profile was similar to that of azathioprine. The majority of side effects were linked to opportunistic infections, the blood system, and the gastrointestinal tract. After kidney and most likely other solid organ transplants, MMF provides better immunosuppressive treatment. In the majority of countries, MMF has been licensed since 1995 to prevent acute renal allograft rejection. It has been used in different combinations of immunosuppressive drugs and in various dosages and regimens. [19]

Most patients experienced symptom improvement and were able to lower their prednisone dosage when MMF was added to immunosuppressive regimens. MMF was well received by 10 out of 11 individuals, with little adverse effects reported. These imply that MMF is an effective immunosuppressive medication with little adverse effects for reducing ocular inflammation. [20]

Mycophenolate mofetil (MMF) is an established therapy for systemic sclerosis (SSc), but its pharmacokinetics in this disease remains unexplored. [21]

The prodrug of mycophenolic acid (MPA), mycophenolate mofetil (MMF), was used to treat psoriasis in the 1970s until it was discontinued due to negative effects and concerns about carcinogenesis. Decades later, the prodrug MMF appeared in the transplant industry. Since then, dermatologists have used MMF off-label to treat a variety of inflammatory skin problems. The majority of study has focused on its usage in connective tissue disorders, autoimmune blistering disorders, psoriasis, and dermatitides. MMF's lymphocyte selectivity and resulting lower toxicity profile are the foundation of its allure. It might be a better course of treatment because of these qualities. Currently, the absence of randomised controlled trials, possible unidentified side effects, and treatment costs limit its use in dermatology. [22]

The clinical experiences of two institutions using mycophenolate mofetil (MMF) for severe lupus nephritis are described in a study. Twelve patients with refractory or relapsing nephritis who had previously received cyclophosphamide therapy were included, along with one patient who accepted MMF but declined cyclophosphamide as an initial treatment for diffuse proliferative nephritis. According to the findings, MMF is well tolerated and may be effective in managing the main renal symptoms of systemic lupus erythematosus. To determine the function of MMF in the treatment of lupus nephritis, controlled clinical trials are required. [23]

CLINICAL EVIDENCE SUPPORTING MMF IN VARIOUS AUTOIMMUNE DERMATOSES:

Psoriasis:

Mycophenolate mofetil (MMF) is being evaluated in this trial for the treatment of psoriatic arthritis and persistent plaque psoriasis. For ten weeks, eleven patients—six with psoriatic arthritis and five with plaque psoriasis—received MMF (2 g/day). Although MMF was well tolerated, only three patients with arthritis and mild cases of psoriasis exhibited improvement. Cases of severe psoriasis did not react. Although MMF may help autoimmune diseases due to its immunosuppressive properties, its effectiveness in treating severe psoriasis is still unknown. Larger controlled studies are necessary to ascertain MMF's ideal dosage and effectiveness in treating psoriasis, despite the fact that it shows promise in treating psoriatic arthritis. [24]

Lupus (Systemic & Cutaneous Lupus Erythematosus):

More recent research supports the use of Anifrolumab in cases of recalcitrant CLE, while mycophenolate mofetil has been used as a second and/or third line treatment. Small case studies have shown that MMF is useful in discoid LE, chilblain LE, and SCLE. According to a retrospective analysis of 24 patients with treatment-resistant CLE, 62% of them had resolution or near resolution of disease activity, and all patients displayed some degree of clinical improvement. Furthermore, MMF and hydroxychloroquine were successfully tested together in a short case series including three patients. [25]

Pemphigus:

Mycophenolate mofetil (MMF) is assessed in this trial as a corticosteroid-sparing treatment for pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

With a median remission duration of nine months, 71% (PV) and 45% (PF) of the 42 patients experienced remission. MMF was well tolerated; the most frequent problem was mild gastrointestinal problems, with 77% reporting no negative effects. Although MMF is more costly than azathioprine, it showed a better safety profile. According to the study's findings, MMF is a safe and effective adjuvant treatment for pemphigus that provides a good substitute for corticosteroid therapy, especially for individuals who are intolerant to other immunosuppressants. [26]

Dermatomyositis:

In this trial, juvenile dermatomyositis (JDM), a rare inflammatory illness of the muscles and skin, is treated with mycophenolate mofetil (MMF). After receiving MMF for a year, the skin and muscular disease activity ratings of fifty youngsters significantly decreased. The dosage of prednisone was reduced, which encouraged better growth. MMF was well accepted and had no serious side effects; infection rates were steady at first but decreased after 7 to 12 months. According to the results, MMF is a useful treatment for JDM that reduces corticosteroid reliance and improves disease symptoms while preserving drugs. To verify its long-term safety and effectiveness, more randomized trials are necessary. [27]

Vitiligo:

The effectiveness of topical Mycophenolate mofetil (MMF) in treating vitiligo was evaluated in this pilot trial. For three months, thirty patients administered MMF 15% twice a day. 36.6% had 25% repigmentation by the third month, with greater outcomes in locations that were exposed to the sun. There were no documented adverse effects. MMF, however, was ineffective in circumstances where the patient was steroid resistant and less efficacious than strong steroids. Although the immunosuppressive qualities of MMF point to some advantages, more extensive research is required. For people who are unable to use steroids, MMF may be a safe substitute. Its medicinal effects could be improved by increasing skin penetration. [28]

Alopecia Areata:

This case study details a 14-year-old girl who began using enteric-coated Mycophenolate sodium (EC-MPS) for steroid- and cyclosporine-dependent nephrotic syndrome and experienced alopecia and irregular menstruation. Hair loss started after the second month of medication, but it stopped when the dosage was cut in half. Two months after the dose was changed, the menstrual periods that had stopped started up again. EC-MPS successfully maintained illness remission in spite of these adverse effects. This is the first instance of adolescent EC-MPS being linked to baldness and irregular menstruation. The study indicates that smaller dosages might still be useful in treatment and emphasizes the importance of keeping an eye out for uncommon adverse effects. [29]

Infection Risk Associated with MMF

In individuals with SLE, MMF was found to be significantly associated to an increased risk of overall infection, with an adjusted OR of 1.90 (95% CI 1.48–2.44). Infections of unknown source (adjusted OR 1.73, 95% CI 1.21–2.47), bacterial infections (adjusted OR 2.07, 95% CI 1.55–2.75), viral infections (adjusted OR 1.92, 95% CI 1.23–3.01), and opportunistic infections (adjusted OR 2.13, 95% CI 1.31–3.46) all showed positive correlations. Compared to single infection (adjusted OR 1.89, 95% CI 1.46–2.45), the OR value for complex infection (adjusted OR 2.12, 95% CI 1.39–3.23) was somewhat higher. Using the control group as a reference, the top three infections linked to MMF-related risk for each individual infection were herpes zoster (adjusted OR 2.85, 95% CI 1.32–6.15), urinary tract infection/pyelonephritis (adjusted OR 3.14, 95% CI 1.94–5.11), and bacteremia/septicemia (adjusted OR 3.16, 95% CI 1.29–7.76). [30]

The Centres for Disease Control and Prevention (CDC) standards defined BSI as the isolation of a bacterial or fungal pathogen from a blood culture that was not linked to contamination, unless the contaminant was isolated twice or more in a two-day period.

in addition to infection-related clinical signs. Coagulase-negative staphylococci, non-hemolytic streptococci of the viridans group, Aerococcus spp., Cutibacterium spp., Bacillus spp. (not Bacillus anthracis), Corynebacterium spp. (not Corynebacterium diphtheria), and Micrococcus spp. were regarded as contaminants. [31]

Table 2 Associations between MMF use and risk of infection in patients with SLE

Variable	MMF users (N = 376)	Non-users (N = 2963)
No infection	122 (32.4)	1640 (55.3)
Overall infection	254 (67.6)	1323 (44.7)
Single infection	206 (54.8)	1111 (37.5)
Complex infection	48 (12.8)	212 (7.2)
Bacterial infection	147 (39.1)	765 (25.8)
Urinary tract infection/pyelonephritis	38 (10.1)	138 (4.7)
Pneumonia	97 (25.8)	571 (19.3)
Encephalitis/meningitis	2 (0.5)	19 (0.6)
Endocarditis/myocarditis	2 (0.5)	8 (0.3)
Septic arthritis/osteomyelitis	0 (0)	3 (0.1)
Septicemia/bacteremia	8 (2.1)	29 (1.0)
Virus infection	36 (9.6)	207 (7.0)
Herpes zoster	11 (2.9)	38 (1.3)
HCMV infection	2 (0.5)	16 (0.5)
EBV infection	14 (3.7)	68 (2.3)

HPV infection	0 (0)	4 (0.1)
Virus hepatitis	4 (1.1)	61 (2.1)
Opportunistic infection	31 (8.2)	132 (4.5)
Tuberculosis	9 (2.4)	47 (1.6)
Systemic mycoses	22 (5.9)	89 (3.0)
Other infections of unknown cause	63 (16.8)	318 (10.7)
Upper respiratory infection	53 (14.1)	297 (10.0)
Skin or mucosal infection	22 (5.9)	92 (3.1)

The data derived from three pivotal trials established the safety and tolerability of MMF in adult renal transplantation recipients. Invasive cytomegalovirus (CMV) infections were more common with MMF than with AZA, according to all three pivotal trials, particularly in patients taking a higher dose of MMF (3 g/d). At six months, a year, and three years after transplantation, the incidence of CMV infection was likewise greater with MMF 2 g/d than AZA, but this difference was not statistically significant. [32]

Adverse events of the FK506 plus MMF regimen:

The transplant recipients who used the FK506 accompanied with MMF regimen during the follow-up period in each trial had a 9.6% (95% CI 5.5-16.4%) risk of mortality, whether or not it was attributable to the use of the immunosuppressive regimen. 39.9% (95% CI 19.9-64%) of patients experienced at least one adverse event linked to the immunosuppressive regimen. Gastrointestinal symptoms (diarrhea, vomiting, and nausea), infections, renal failure, and hematological abnormalities (leukopenia, anemia, and thrombocytopenia) were the most commonly reported side effects. [33]

Table 2 - Summary of the risk of occurrence of the main adverse events associated with the FK506 associated with MMF immunosuppression regimen.

Adverse event	Risk (%)	CI 95%
Anemia	8.8	3-23
Leukopenia	16.8	9.3-28.6
Thrombocytopenia	7.6	2.9-18.6
Infections	26.4	10.9-51.4
CMV infection	9.2	5.9-14
Acute kidney injury	39.7	8.4-82.7
Diabetes	23.5	13.8-37.1
Diarrhea	16.1	8.5-28.2
Nausea	4.8	4-38

Future Directions and Emerging Research:

MMF has been shown to have a steroid-sparing effect and to be helpful in sustaining remission. MMF has become a significant new treatment option for FSGS and pediatric nephrotic syndrome. [34]

An immunosuppressive medication called mycophenolate mofetil (MMF), which was first prescribed to transplant recipients to avoid graft rejection, has shown promise as a treatment-naïve AIH patient . By specifically preventing the de novo synthesis of guanosine nucleotides, which is essential for the growth of B and T lymphocytes, MMF suppresses the proliferation of lymphocytes . Compared to AZA, this approach has theoretical advantages that could result in fewer side effects and better patient compliance. Numerous research, including meta-analyses, have indicated that MMF is useful in causing and sustaining remission in individuals with AIH, even those who have never received therapy. [35]

Novel formulations of MMF:

In many clinical contexts, the absence of commercially available oral liquid dose forms is a persistent issue. For (i) children; (ii) patients who cannot swallow solid dosage forms like tablets or capsules; (iii) patients who need to receive medications via nasogastric or gastrostomy tubes; and (iv) patients who need non-standard doses that are easier and more accurately measured by using a liquid formulation, a pharmacist is frequently faced with the challenge of providing an impromptu oral liquid.

MMF comes in 250 mg capsules and 500 mg tablets for oral use. The 200 mg/mL suspension form (Roche Products Ltd., UK) is made in other countries but is not available in Iran. This product's low demand, high cost ($299), and the toxicity of the crushed tablets make pharmacist involvement necessary to maintain compounding abilities.

A vertical flow hood was used to prepare an MMF suspension at a concentration of 50 mg/mL. Six 250 mg capsules or three 500 mg tablets were poured into a mortar, then wetted and triturated with 7.5 mL of Ora-Plus to create a smooth paste. After adding 15 mL of simple syrup, the mixture was further triturated. After that, the contents were put into an amber container and mixed with simple syrup to reach a final volume of 30 mL. Next came the addition of cherry essence. The bitter taste of the medication is lessened by the cherry flavor. [36]

Biomarkers for infection risk prediction:

In order to prevent graft rejection, recipients of solid-organ transplants need long-term immunosuppression, which raises their risk of infection. In order to better predict infection risk in this cohort, we set out to find indicators of infection risk in pediatric solid-organ transplant recipients. In a single-center

registry study, 20 liver transplant patients and 75 kidney transplant patients were examined. As part of standard-of-care, immunologic labs, such as vaccine titers, immunoglobulins, and lymphocyte subsets, were obtained every six months. Immunosuppressive regimens and the number of infections were noted at the appropriate times. A linear mixed-effects regression model was used to ascertain the relationship between immunological parameters and the frequency of infections. The 2-sample t-test was used to examine the relationship between drugs and immunological markers. [37]

Conclusion:

Mycophenolate mofetil (MMF) has firmly established itself as a critical component of immunosuppressive therapy, particularly in the management of solid organ transplantation and a diverse range of autoimmune diseases. Its targeted mechanism, focused on the inhibition of inosine monophosphate dehydrogenase, results in selective suppression of lymphocyte proliferation, contributing to both reduced rates of allograft rejection and effective disease control in autoimmune contexts. Clinical evidence consistently demonstrates that MMF, especially in combination with agents like cyclosporine and corticosteroids, not only improves graft survival but also offers a steroid-sparing benefit, broadening its clinical appeal. Despite these strengths, MMF's potent immunosuppressive effects heighten patient vulnerability to a wide array of infections—including bacterial, viral, and fungal pathogens—necessitating careful risk assessment and proactive management strategies. The adverse event profile, primarily involving gastrointestinal discomfort and cytopenias, further underlines the need for individualized dosing and regular monitoring. Optimizing the balance between therapeutic efficacy and safety is paramount for maximizing patient outcomes. Recent advances—such as new formulations, expansion to pediatric and rare autoimmune indications, and the application of immunologic biomarkers for infection risk stratification—promise to further refine and personalize the use of MMF. Nevertheless, significant questions remain regarding long-term safety in emerging applications, ideal dosing strategies, and the development of robust protocols to minimize infectious complications without undermining immunosuppressive efficacy. In summary, MMF stands as a cornerstone of modern immunosuppressive regimens. Its continued success will depend on ongoing research efforts, multidisciplinary clinical vigilance, and the integration of emerging innovations to ensure that patients receive the most effective and safest possible care.

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