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Article abstract

Precision medicine can put clinicians in a position where they must act more as resource allocators than their traditional role as patient advocates. In the allocation of transplantable organs and tissues, the use of eplet matching will enhance precision medicine but, in doing so, generate a tension with the present reliance on rule of rescue and justice-based factors for allocations. Matching donor and recipient human leukocyte antigens (HLA) is shown to benefit virtually all types of solid organ transplants yet, until recently, HLA-matching has not been practical and was shown to contribute to ethnic/racial disparities in organ allocation. Recent advances using eplets from the HLA molecule has renewed the promise of such matching for predicting patient outcomes. The rule of rescue in organ allocation reflects a combination of ethical, policy, and legal imperatives. However, the rule of rescue can impede the allocation strategies adopted by professional medical associations and the optimal use of scarce transplant resources. While eplet-matching seeks to improve outcomes, it may potentially frustrate current ethics-motivated initiatives, established patient-practitioner relationships, and functional conventions in the allocation of medical resources such as organ and tissue transplants. Eplet-matching allocation schemes need to be carefully and collaboratively designed with clear, fair and equitable guidelines that complement functional conventions and maintain public trust.

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The Rule of Rescue in the Era of Precision Medicine, HLA Eplet Matching, and Organ Allocation

Blake Murdoch[a], Darren N. Wagner[a], Shaifali Sandal[b,c], Karen Sherwood[d]

Résumé

La médecine de précision peut placer les cliniciens dans une position où ils doivent agir davantage comme des répartiteurs de ressources que dans leur rôle traditionnel de défenseurs des patients. Dans l'attribution d'organes et de tissus transplantables, l'utilisation de l'appariement eplet renforcera la médecine de précision mais, ce faisant, créera une tension avec la dépendance actuelle au devoir d'assistance et des facteurs fondés sur la justice pour l'attribution des ressources. L'appariement des antigènes leucocytaires humains (HLA) du donneur et du receveur est bénéfique pour pratiquement tous les types de greffes d'organes solides. Pourtant, jusqu'à récemment, l'appariement HLA n'était pas pratique et il a été démontré qu'il contribuait aux disparités ethniques/raciales dans l'attribution des organes. Des avancées récentes utilisant des eplets de la molécule HLA ont renouvelé la promesse d'un tel appariement pour prédire les résultats pour les patients. Le devoir d'assistance dans l'attribution d'organes reflète une combinaison d'impératifs éthiques, politiques et juridiques. Cependant, le devoir d'assistance peut entraver les stratégies d'attribution adoptées par les associations médicales professionnelles et l'utilisation optimale des ressources limitées en matière de transplantation. Alors que l'appariement d'eplet cherche à améliorer les résultats, il peut potentiellement contrecarrer les initiatives actuelles motivées par l'éthique, les relations établies entre patients et praticiens et les conventions fonctionnelles dans l'attribution des ressources médicales telles que les transplantations d'organes et de tissus. Les systèmes d'attribution de l'eplet doivent être conçus avec soin et en collaboration, avec des lignes directrices claires, justes et équitables qui complètent les conventions fonctionnelles et maintiennent la confiance du public.

Mots-clés

don et transplantation d'organes et de tissus, allocation des ressources, devoir d'assistance, appariement HLA, médecine personnalisée

Abstract

Precision medicine can put clinicians in a position where they must act more as resource allocators than their traditional role as patient advocates. In the allocation of transplantable organs and tissues, the use of eplet matching will enhance precision medicine but, in doing so, generate a tension with the present reliance on rule of rescue and justice-based factors for allocations. Matching donor and recipient human leukocyte antigens (HLA) is shown to benefit virtually all types of solid organ transplants yet, until recently, HLA-matching has not been practical and was shown to contribute to ethnic/racial disparities in organ allocation. Recent advances using eplets from the HLA molecule has renewed the promise of such matching for predicting patient outcomes. The rule of rescue in organ allocation reflects a combination of ethical, policy, and legal imperatives. However, the rule of rescue can impede the allocation strategies adopted by professional medical associations and the optimal use of scarce transplant resources. While eplet-matching seeks to improve outcomes, it may potentially frustrate current ethics-motivated initiatives, established patient-practitioner relationships, and functional conventions in the allocation of medical resources such as organ and tissue transplants. Eplet-matching allocation schemes need to be carefully and collaboratively designed with clear, fair and equitable guidelines that complement functional conventions and maintain public trust.

Keywords

organ and tissue donation and transplantation, resource allocation, rule of rescue, HLA eplet-matching, personalized medicine

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INTRODUCTION

During the COVID-19 pandemic, triaging decisions with limited medical resources and life-and-death outcomes prompted closer scrutiny of the ethical, practical, and legal issues surrounding the rule of rescue (1-3). Described as "the imperative people feel to rescue identifiable individuals facing avoidable death" (4), the rule of rescue is an important phenomenon in the context of medical care. In healthcare systems with limited resources, this bias towards saving identifiable patients in distress can come at the expense of other "faceless" patients and can potentially cause significant net harm on a population-wide scale. The rule of rescue is borne out of ethical and legal obligations, and possibly psychosocial impulses (4,5). The ethical obligations derive from both social values about the importance of human life and ethical training provided to healthcare professionals. The legal obligations, which we explore here, stem from fiduciary duties, common law torts, and regulatory standards imposed on healthcare professionals. In pressing situations of resource scarcity, the ethical and legal grounds of the rule of rescue can quickly erode. The justification for the rule of rescue is further cast into question by emerging technologies associated with precision medicine.

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Recent advancements in eplet matching research promise to generate new and more precise allocation methods in organ and tissue donation and transplantation (OTDT). The growing influence of such precision medicine, which includes eplet matching for transplant allocation, creates tensions with the rule of rescue and justice-based reasoning that are conventionally important in healthcare settings with resource scarcity and critically ill patients, such as those needing OTDT. Here we explain eplet matching and its importance, discuss the legal and ethical foundations of the rule of rescue, and examine the emerging challenge that eplet-matching potentially poses to the rule of rescue in allocation.

PRECISION MEDICINE AND ALLOCATION

Precision medicine focuses on interventions based on individual characteristics of each patient, often by targeting an individual's specific genetics and biochemistry (6). Precision medicine methods hold significant promise in several areas of medicine, including improving OTDT outcomes through epitope matching (5), and developing drug treatments for certain gene-related forms of cancer (7). The potential of precision medicine to affect the allocation of healthcare resources is theoretically immense. Some commentators have predicted a future medical provision that allocates healthcare resources through a complex algorithmic process that tailors' treatments "to the characteristics of the specific individual in the spirit of precision medicine" (8). This development could take informed decision-making mostly out of clinicians' hands, as the data and logic used could become incredibly complex. There is also the possibility or even likelihood of allocation systems advancing beyond mere algorithms and incorporating artificial intelligence (AI) that engages in machine learning, i.e., independent iterative self-modification that could make the logic and underlying data utilization opaque to physicians. Whether these systems are allowed to develop and function as described is the source of ongoing debate. While this is not the focus of our manuscript, such AI raises many ethical issues, which are engaged by key AI ethics policies such as the 2018 *Montreal Declaration on Responsible Development of Artificial Intelligence* (9). Regarding interpretability, some AI researchers are focusing on developing interpretable AI platforms to help healthcare professionals understand the logic underlying algorithmic decision-making (10).

While some argue that precision medicine enhances the traditional patient-centred ethos of healthcare provision (11), certain implications of precision medicine may complicate such aims. For example, in the context of allocating scarce medical resources, strictly data-driven allocations of precision medicine can diminish a decision-maker's ability to duly consider such value-based factors as principles of equity and justice. This could then restrict clinicians to acting more as objective resource allocators than their traditional role as patient advocates – precision medicine is thus potentially at odds with the rule of rescue.

Precision medicine in the context of scarce resource allocation already exists to a limited extent. In the field of rare disease, there are a growing number of costly therapies with precision targeted approaches. In these scenarios, physicians must often implement allocation policy at point of care (12). In the context of organ allocation, precision epitope-matching systems are being developed, presenting both potential benefits and challenges to conceptions of fairness in allocation and waitlist policy. These systems could put the codified medico-legal primacy of the patient into question. Some current allocation models, such as the model for end-stage liver disease (MELD), are designed for patient-centred allocations based on highest mortality risk (13,14). This model has already "mostly eliminated the transplant clinician's abilities to exaggerate a patient's disease severity in order to move 'up' the patient's place on the transplant list," something many would consider an improvement in ethical allocation (14). The United Network for Organ Sharing (UNOS) is exploring newer precision allocation systems (15). However, the push towards precision allocation tools can obscure the patient-physician role. As one article about this issue warns, the increased complexity of allocation tools such as innovative biomarkers may "limit the enthusiasm of transplant physicians" (16).

EPLET MATCHING – A PRIMER

In solid organ transplantation, which involves a donor's organ engrafted into a recipient, the donor's human leukocyte antigens (HLA) are the primary alloantigens recognized by the recipient's immune system. HLA mismatches between the donor's and recipient's antigens are therefore associated with a higher risk of sensitization, graft failure and rejection (17,18). The benefits of HLA matching have been demonstrated in virtually all types of solid organ transplants and HLA matching provides numerous benefits, including better and longer graft survival (19). As such, matching donors and recipients for these molecules has been a central tenet of organ allocation. However, HLA matching is particularly rare due to the overwhelming number of HLA variants – HLA genes are the most polymorphic in the human genome (20). HLA matching is thus currently not a priority in allocating critical organs such as hearts, livers, and lungs, and has also been devalued in a stepwise manner in kidney allocation algorithms (21-23). One reason for the devaluing of HLA matching in these allocation schemes is the introduction of modern immunosuppression, which decreased the risk of acute rejection (24). HLA matching, especially HLA-B, was also shown to be contributing to ethnic and racial disparities in access to transplantation (25,26).

Recent developments in structural immunology and precision medicine have, however, allowed researchers to evaluate an alternative approach. There is growing recognition that molecular differences at the antibody-accessible (surface) region of the HLA molecule determine antigenicity and can cause organ rejection. Epitopes are large surface areas where anti-donor antibodies can bind and are commonly referred as to Structural Epitopes. Within each structural epitope is a short sequence of one or more polymorphic amino acids that are directly implicated in the immune response to the allograft. This short sequence of amino acids is called a Functional Epitope, or Eplet. By breaking down each donor HLA molecule into a series of mismatched eplets, the degree of match between donor and recipient can be examined more granularity. Evolving work from several groups around the world is demonstrating that eplet matching (especially at HLA-DR and -DQ) can decrease the risk

of rejection and has an impact in graft survival (27-32). Knowledge of the level of eplet mismatch at the time of transplant can not only serve as a useful predictor of post-transplant risk of alloreactivity but also inform adjustments of immunosuppression when patients develop other complications, such as infectious or malignant complications. More importantly, because immunosuppression complications are some of the leading causes of patient death post-transplantation, precise identification of the eplet mismatch level is potentially of critical importance, both in the pre-transplant accessibility of offers and in the post-transplant risk stratification of alloreactivity to the graft.

THE RULE OF RESCUE AND ORGAN ALLOCATION

The rule of rescue is more than a concept – it is an observed reality. One study about allocation of intensive care unit beds found that the rule of rescue was often relied upon because clinicians perceived strong ethical obligations to "identifiable living patients" (33). A 2020 survey of emergency physicians found that "emergency department triage decisions are more informed by the patient's acute presentation" than "by factors associated with the perceived risks and benefits of ICU care" (34). In that survey, emergency physicians highlighted that "established institutional triage criteria and protocols are infrequently applied" (34). In other words, the rule of rescue can undermine carefully calculated and considered polices on allocating medical resources.

Rationing and allocating scarce medical resources such as solid organs has recently sparked new bioethical debates and political controversies (35,36). Allocation policies and the application of the rule of rescue are prevalent and contentious issues, even among transplant recipients and candidates (37). For medical professionals, such life-and-death resource allocations are fraught with moral and pragmatic tensions that include equitable treatment, efficient outcomes, and assisting those most in need (38). Some bioethicists have criticized allocation based on the rule of rescue as "worst-off prioritarianism" (35), which undercuts other allocation principles such as utilitarian ideas of greatest benefit (based on cost-benefit analyses) and egalitarianism, which aims to provide "fair chances" to all patients (39). In 2006, The UK's National Institute for Health and Care Excellence (NICE) published their deliberations on whether the rule of rescue should be rejected as a basis for medical provision (40). At that time, a majority of NICE believed "it should be applied in certain exceptional cases" that met a series of criteria (40). Despite their concerted deliberations and careful policies on this issue, NICE has been criticized for inconsistencies in their approach to the rule of rescue (41). To provide much-needed guidance and consistency for organ allocation in the United States, UNOS developed rationing policies based on organ-specific criteria, including waitlist times, illness severity, prognostic indicators, and human leukocyte antigen compatibility (38). Nevertheless, transplantation specialists sometimes allocate organs according to the rule of rescue (42).

RULE OF RESCUE IN LAW AND PROFESSIONAL ETHICS

The rule of rescue derives largely from a combination of ethics, policy, and law (5). The ethical precepts undergirding the rule of rescue include core medical traditions, such as the Hippocratic Oath. However, it is the legal obligations that form binding requirements, and which substantiate the ethical and policy pressures that reinforce the rule of rescue. In most Commonwealth countries (including Canada), in the US, and many other jurisdictions, physicians have fiduciary obligations to act in the best interests of their patients. The obligation partly reflects the physician-patient power balance, in which the patient is "peculiarly vulnerable" to their physician's behaviours and decisions (43,44). This strong obligation can include a requirement for physicians to prioritize the interests of identifiable patients above broader concerns such as cost containment (45,46).

Another obligation is the duty of care, which derives from tort law. Physicians must adhere to a standard of care that includes reasonable skill, care, and judgment or they risk tortious liability through negligence. However, so-called defensive medicine can arise, particularly in more litigious jurisdictions like the United States, when practitioners make decisions to avoid legal liability rather than in accordance with best practice, professional guidelines, or patient outcomes. While a patient's physician owes a duty of care, so too can their healthcare institutions, which are potentially liable for damages sustained due to improper protocols (47). Defensive medicine can also encourage more extreme forms of patient advocacy, such as exaggerating the condition of a transplant candidate in hopes of securing scarce organs or tissues (48,49). This kind of zealous advocacy for a patient can impede the equitable and effective allocation of organs and tissues.

Self-regulating colleges of physicians and surgeons have largely internalized the legal obligations imposed on physicians by transcribing them into codes of ethics, policy guidelines, and standards of practice. The American Medical Association (AMA) asserts that physicians are responsible for contributing to fair allocation policies that are explainable to patients and the public, and that respond to such criteria as medical need and benefit; lifesaving and quality of life enhancing; and objective, flexible, and transparent decision making (50). For allocating any limited medical resource, the AMA's Code of Medical Ethics highlights five criteria: "likelihood of benefit, urgency of need, change in quality of life, duration of benefit, and the amount of resources required for successful treatment" (51). The Organ Procurement and Transplantation Network, which oversees OTDT in the US, issued a white paper that identified three core principles for allocating organs, including utility, justice, and respect for persons and their autonomy (52). Similarly, the Canadian Medical Association (CMA) requires that physicians participating in transplantations allocate organs in an ethically sound fashion (53). To assist physicians, the CMA has instituted a set of guiding principles for OTDT that centre on justice, equal opportunity, and utility (54). However, the CMA admits that for OTDT allocations "these principles are often in conflict" (55). For instance, a utilitarian goal such as saving the most lives or maximizing quality-adjusted life years can be at odds with aims such as equality or justice that attempt to address medical comorbidities resulting from social inequities (56). Yet, highly detailed guidance for how to resolve complex problems of

conflicting principles can be lacking, which can leave crucial decisions to physician discretion. While professional discretion is a necessary reality for many aspects of medical practice, gaps or uncertainties in allocation protocols could heighten physicians' fear of liability and a tendency towards defensive medicine, consequently bolstering the influence of the rule of rescue in these critical allocations.

EFFECTS OF EPLET MATCHING & SHIFTING AWAY FROM RULE OF RESCUE

The clinical situation might dictate which rule will prevail. In a situation where patient death is imminent in the absence of a transplantation, the rule of rescue will likely prevail over eplet matching. This kind of situation includes most critical organs, such as liver, lung, heart, and, in some circumstances, kidney. Nevertheless, eplet matching may take precedence in other situations and in patients, such as the highly sensitized, for whom it is difficult to allocate offers under the current allocation system. For instance, eplet matching may take priority in most kidney transplantations and when a living donor is involved. Most cases of kidney transplantation are not emergencies, as patients can survive on dialysis for months. Likewise, some heart and lung transplantations may also become less urgent as new supportive devices are introduced. These less-urgent transplantations are opportunities for exploring eplet matching in allocation schemes and for implementing allocation rules based on utilitarianism and egalitarianism, rather than the rule of rescue. Living donation, meaning donation by a living individual who can survive without the donated tissue (e.g., kidney, liver lobe), is another field of transplantation where maximizing the expected survival of the organ may take precedence. Several new programs for living donation are already exploring allocation schemes that rely less on the rule of rescue. For example, inviting compatible donors to participate in the paired kidney donor exchange program increases the opportunity for pairing with a better HLA matched offer (57), or in the advance kidney donation program, a living donor donates their organ well in advance to the intended recipient's moment of need for that organ (58).

The implementation of eplet matching in organ allocation may limit opportunities for practitioners to exercise professional discretion. The specific manner of implementation will determine the extent of remaining professional discretion. Relying on information and criteria derived from eplet matching may result in more efficient organ allocations with better overall outcomes, with the side effect of significantly curtailing practitioner advocacy for patients. It is possible that this side effect could diminish human-centred patient care and affect both outcomes and the psychological experiences of recipients; a diminished ability for practitioners to exercise discretion to espouse ethical principles; and less understanding of organ allocation reasoning for both patients and practitioners (59).

Beneficial outcomes from precision medicine have been constrained because many technologies are still in the early stages of development (60). Placing too much importance on eplet matching without fully considering the effects on fairness might undercut current organ allocation systems and ethical norms (59). What constitutes the best possible care continues to be debated, especially as ethical consideration about quality of life continues to evolve. Eplet matching represents one of several variables that can be used in developing allocation algorithms.

Using precision medicine to inform allocation models will potentially reduce the opportunity for individual practitioners motivated by the rule of rescue to unduly influence who receives an organ first (61), especially since some practitioners stray from set policies and guidelines (62). OTDT organizations have stressed the need for consistency in allocation systems and their application (63). However, many medical resource allocation systems inconsistently apply cost-utility analyses (64). Carefully implemented eplet matching systems could introduce another objective metric for allocations, thereby helping improve consistency and fairness.

The ethical principles that guide organ allocation policies – such as justice, equal opportunity, respect for personal autonomy, and utility – might best be served by carefully designed models based on precision medicine that continue to weigh other factors as well. Ideally, these models should not increase wait times for any candidate. As precision medicine gains influence in organ allocation, practitioners and policymakers should particularly scrutinize issues about equity in access, including whether certain groups have poorer candidacy chances due to social determinants of health, racial background, or ethnic group (65). Several metrics show that wealthy individuals who are not visible minorities have better outcomes in OTDT than racialized and/or economically marginalized individuals (66-68). Crucially, there remains uncertainty about whether eplet matching will level or, like HLA matching, exacerbate allocation disparities along racial lines. Implementation of eplet matching in clinical practice requires a thorough analysis of the implications, particularly with respect to equity, the input of a wide range of stakeholders, and a pilot/transition period. A recent online public deliberation conducted with members of the Canadian public underscored several thematic concerns in implementing eplet compatibility in kidney transplantation: health maximization, mitigation of negative impacts, principles of fairness, evidence-based healthcare, and responsibility to maintain trust (69). Participants mentioned the need for flexibility, accountability, transparent communication, and a transition plan. It behooves policymakers and practitioners to ensure the implementation of algorithm-driven systems that prioritize utility do not exacerbate treatment inequities.

CONCLUSION

Eplet matching seeks to improve OTDT outcomes by tailoring interventions to the specific biological characteristics of individual patients. However, if implemented without due ethics and policy consideration, eplet matching may potentially frustrate current ethics-motivated initiatives, impair established patient-practitioner relationships, and impede functional aspects of resource

allocation. Therefore, the introduction of eplet-based allocation schemes needs to be careful, intentional, and collaborative (47). Special care should be given to the legality of new allocation systems, which may require changes to regulation, ethical guidance, and/or professional practice standards. Having clear, fair, and equitable guidelines is essential to maintaining public trust, organ supply, and the proper operation of allocation systems (70,71).

In keeping with the ethical tenets set out in professional guidelines, eplet-based allocation regimes should use a well-defined framework that pursues such guiding principles as justice, equal opportunity, personal autonomy, transparency and utility. While making continued efforts to address the shortage of donations, professional medical bodies should embrace the potential of eplet matching to predict better patient outcomes and resource allocation. In the ongoing effort to use health care resources prudently and effectively (71), any further shift towards algorithmic decision-making should be tempered by ethical principles within the health care profession, social values respecting basic human rights, and the highest ethical standards (56,72,73). Such considerations will be key to retaining patient-centred care and some degree of physician advocacy for transplant candidates and recipients. While physicians championing their patients' wellbeing can disrupt allocation systems, such physician advocacy is also emblematic of the highest virtues in modern medicine – care and compassion. Fortunately, these virtuous ends are not necessarily antithetical to more effective and precise allocation schemes, which can be designed to complement the patient-physician relationship and improve population-level outcomes.

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