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SECOND THOUGHTS

Undocumented Immigrants Face a Unique Set of Risks from Tuberculosis Treatment: Is This Just?

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Consider a hypothetical scenario: Rosa, a 35-year-old healthy woman, visits a primary care physician at a community clinic for a routine checkup. She immigrated to the United States one year ago from Mexico, a country with a higher prevalence of tuberculosis (27 cases per 100,000 people) [1] than the US [2]. The primary care physician recommends screening for latent tuberculosis infection (LTBI) based on established guidelines. Rosa's purified protein derivative (PPD) skin test is positive, and she is started on isoniazid (isonicotinylhydrazide or INH). While taking it, she develops jaundice and lower extremity edema and is admitted to the hospital. She becomes critically ill and is found to have fulminant hepatic failure—acute liver failure—an iatrogenic consequence of INH treatment. A liver transplant would save her life, but Rosa is deemed not to be a good candidate for transplant because she is poor, uninsured, and undocumented. She dies of liver failure and sepsis. Here we consider the unique risks that undocumented immigrants incur when accepting LTBI therapy and the physician's duty to disclose these risks, and we present policy and clinical solutions that would protect public health without placing undue burden on undocumented immigrants.

LTBI screening and treatment serve a dual purpose of preventing reactivation of tuberculosis (reactivation TB) in the individual and protecting public health by preventing the spread of TB in the community. Although 9,421 new TB cases were reported in the US in 2014, an estimated 11 million people in the US are living with LTBI [2, 3]. The lifetime risk of reactivation TB in those with LTBI is 10 percent, but identification and treatment of LTBI can reduce the risk of active disease by 60-90 percent [4-6].

LTBI screening and treatment are particularly important for immigrants from regions where TB is common. Over half (66 percent) of US LTBI cases occur in people born outside the US, and the case rate of reactivation TB among that group is about 13 times higher than among persons born in the US [2]. The Centers for Disease Control and Prevention (CDC) recommend LTBI screening for all immigrants from high-prevalence countries who have lived in the US for less than five years [7]. There were approximately 7 million new immigrants in the US in 2010, including approximately 2.7 million from three high-prevalence countries: Mexico, China, and India [8]. This population also includes 1.8-2.3 million undocumented immigrants [9, 10]; these are immigrants who

either entered the US without legal documentation or who entered legally but have since violated the terms of those documents. Over half of this cohort originated in countries with a high prevalence of TB [9, 10].

The antibiotic INH, the current preferred treatment for LTBI [7], carries a small but measurable risk of hepatotoxicity and hepatic failure. Up to 20 percent of patients receiving INH will have mild subclinical liver injury or elevated liver transaminases, and 0.2-0.5 percent will have serious and potentially fatal hepatotoxicity [5, 11]. The fatality rate for INH-induced hepatitis (5-10 percent) increases with age and alcohol use [12, 13]. Alternative regimens for LTBI include rifampin, which has less (but not zero) risk of hepatotoxicity as well as a shorter treatment duration (four to six months rather than nine months with INH) and improved adherence [14, 15]. However, it is not widely used due to cost, interaction with other medications, lack of large prospective randomized studies, and concerns over development of rifampin-resistant TB [16].

Treatment for INH-related liver failure might require liver transplantation, which is rarely available to undocumented immigrants [17, 18]. They are not explicitly ineligible for transplant [17], but ability to pay for posttransplant care, often understood in terms of whether one has health insurance, may be considered when determining transplant eligibility (i.e., listing decision) [19], and an estimated 63 percent of undocumented immigrants are uninsured [9]. Undocumented immigrants are not eligible for most federal, means-tested public benefits such as Medicaid or marketplace exchange insurance plans established by the Patient Protection and Affordable Care Act [20]. The only federal, means-tested public insurance program available to undocumented immigrants is Emergency Medicaid, which does not cover organ transplantation [20, 21]. Accordingly, while all uninsured people face barriers to transplant listing, undocumented immigrants—by virtue of being ineligible for Medicaid and marketplace plans—are at a greater disadvantage.

Legal and Ethical Analysis

Physicians have the responsibility to act in the best interests of their patients. This responsibility requires that physicians help patients make decisions that align with their own values. Physicians who inform undocumented immigrant patients with LTBI about risks of INH-related liver failure but neglect to describe the likely unavailability of the only treatment for that failure (liver transplantation) are not informing members of this patient population to make decisions based on relevant risks. Since not all patients with LTBI have equal access to transplants, physicians who recommend INH treatment are asking undocumented uninsured patients to incur greater risk than persons eligible for transplantation. There is no ethical basis for this disparate treatment.

Physicians must also consider public health and safety in their practices, at least as mandated by state and federal law. Protecting public health is why patient

confidentiality, otherwise sacred, may be breached when the patient poses clear and substantial danger to himself or an identifiable third party [22, 23]. It is also why patients may be quarantined during a declared public health emergency [24, 25]. However, unless defined by statute (and most medical cases are not circumscribed by public health law), it is less clear when patient privacy, liberty, and autonomy may be superseded by public welfare. At present, treatment of LTBI is *not* required by public health departments but is instead strongly encouraged, both for the benefit of the person at risk of reactivation TB (which can, in and of itself, be fatal) and for public health [7].

These benefits—both to the patient and to society—must be considered in the context of the personal risks incurred when the patient undergoes treatment. Because liver failure is a risk of INH treatment and uninsured undocumented patients, due to their lack of health insurance, are generally ineligible for transplant, they are asked to put themselves at greater risk when accepting INH treatment than those eligible for transplant. Whereas other uninsured people, including US citizens, may be denied listing for transplant due to insurance status, they have the opportunity to change that status by participating in marketplace plans or spending down assets to qualify for Medicaid. Undocumented immigrants are unique in that, unless they find employer-sponsored insurance or live within a limited number of regions with nonfederal public insurance programs that are open to all low-income residents [18], they are, under the current framework, *uninsurable*.

With any public health effort that requires risk to the individual, we must weigh that risk against the risk to the public. The risk to undocumented immigrants with LTBI in undergoing INH treatment, while not high in probability, is high in severity (likelihood of significant harm and/or death) and far more severe than the risk to US-born persons, who are eligible for the treatment that would prevent INH-related liver failure from being lethal. This disparity in risk is unjust.

Recommendations

To resolve this injustice, at a minimum, counseling of undocumented immigrants about INH treatment should include detailed discussion of the risks and benefits that they, in particular, are facing, so that they can make an informed choice about INH treatment. Their physicians should explain whether waitlisting for liver transplantation is available to them when presenting potential adverse effects of INH. There is a risk that some undocumented immigrant patients, after engaging in such an informed consent process, would refuse LTBI treatment, placing themselves, their families, and the public health at increased risk of TB. Policy-based solutions and use of a less hepatotoxic alternative agent, such as rifampin, may be required.

If we as a society want an efficacious system of preventing TB reactivation, we could continue to use INH for the majority of LTBI patients despite its risks. If we also want a

just system, we should protect all patients, regardless of immigration status, from possible adverse effects of INH. This would mean allowing undocumented immigrants with INH-related liver failure to be candidates for liver transplantation, regardless of ability to pay, and insuring them against liver transplant-related costs. In light of the overall efficacy of INH treatment for LTBI and the low probability of INH-related liver failure, such coverage should be feasible and not too costly. One option is to include liver transplant and subsequent posttransplant care for INH-related liver failure as services covered under each state's Emergency Medicaid program, for which undocumented immigrants are eligible. There is a precedent for this: although Emergency Medicaid is usually reserved for inpatient care and follow-up, some outpatient services for nonemergent but life-threatening conditions, such as cancer chemotherapy and radiation or dialysis for end-stage renal disease (ESRD), are covered by some state Emergency Medicaid programs [26].

Another alternative could be to create a TB treatment injury compensation program similar to the National Vaccine Injury Compensation Program (VCIP) [27, 28]. The VCIP, operated by the Health Resources and Services Administration (HRSA), was created not only to protect vaccine manufacturers from litigation and to ensure adequate access to vaccines and cost stability, but also to ensure that patients injured by vaccines have access to compensation [27]. The VCIP covers damages, wrongful death, lost wages, and medical expenses for a specific set of injuries related to vaccines and is funded by a $0.75 tax on all vaccines [27]. The proposed TB treatment injury compensation program would only cover INH-related liver failure, and claims would need to be adjudicated rapidly if they were to influence decisions to transplant. A funding mechanism would need to be created; HRSA has set up a similar fund for compensation for injuries related to "countermeasures" (i.e., vaccines, medications, devices, or other items that are used to prevent, diagnose, or treat a condition, such as pandemic flu or Ebola, that constitutes a public health emergency or security threat) [29, 30]. Tuberculosis is not currently considered a public health emergency, but eliminating it is a national public health priority [31], and the precedent of ensuring compensation for those experiencing individual harm for the public good is now well established. Whether offering coverage through Emergency Medicaid or establishing a compensation fund, these policy-based solutions will require strong physician leadership and partnership with nonmedical organizations to be realized.

A clinical approach for clinicians and health systems to consider is the use of rifampin in LTBI treatment for undocumented patients. As mentioned earlier, rifampin has a lower risk of hepatotoxicity than INH [14, 15], and it is considered an acceptable alternative to the preferred INH regimen [7]. Lacking additional large prospective studies, it is too soon to state conclusively that rifampin is a safer choice than INH and similarly efficacious, but the data are promising [14] and a multicenter randomized control trial is ongoing [32].

The most significant barrier to rifampin for this population may be its cost; in the US, a 30-day supply of rifampin is about ten times as costly as INH [33].

Conclusion

There is no valid reason to ask undocumented immigrants to bear greater risk than US-born persons in the pursuit of eliminating tuberculosis in the US. Physicians should consider using rifampin over INH in LTBI treatment for undocumented immigrants, although even rifampin has a risk of acute liver failure. Whether treating with INH or rifampin, physicians have an obligation to disclose risks of the treatment until society is able to establish a mechanism to ensure equitable access to liver transplant for those with LTBI treatment-related liver failure.

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