

## Real-World Challenges to the Practice of Evidence-Based Medicine

The practice of evidence-based medicine involves integrating clinical expertise with the best evidence available.<sup>1</sup> Pharmacy schools train students to apply evidence obtained from the literature to real-life patient scenarios to optimize drug therapy. However, although evidence-based medicine is the ideal, the “real world” presents unique challenges to this practice.

During summer 2012, one of us (R.M.) participated in research involving patients with cystic fibrosis. In this patient population, chronic colonization with *Pseudomonas aeruginosa* is associated with a more rapid decline in lung function<sup>2</sup> and increased mortality.<sup>3</sup> Guidelines recommend long-term use of tobramycin by inhalation to improve lung function and reduce exacerbations in those with chronic *P. aeruginosa* colonization.<sup>4,5</sup> According to an informal telephone survey of cystic fibrosis clinics across Canada, doses for inhaled tobramycin range from 160 to 300 mg bid on a month-on, month-off schedule. The product used for inhalation is either tobramycin solution for inhalation (300 mg in 5-mL volume) or tobramycin for injection (80 mg in 2-mL volume). To find evidence regarding appropriate dosage, we conducted a literature search (with no restrictions) in the PubMed, International Pharmaceutical Abstracts, and Embase databases, with search terms “tobramycin”, “tobramycin solution for inhalation”, “cystic fibrosis”, “eradication”, “chronic colonization”, and “*Pseudomonas aeruginosa*”. The results of the search indicated that the product predominantly studied and shown to be effective was tobramycin solution for inhalation at a dose of 300 mg bid. Why, then, does practice not always reflect this evidence?

A unique concern with the sputum of patients with cystic fibrosis is that certain concentrations of drug are required to not only reach the target (*P. aeruginosa*), but also kill that target. When administered via inhalation, tobramycin, a positively charged molecule, binds to negatively charged glycoproteins in the sputum.<sup>6,7</sup> It has been determined that administration of a certain amount of the drug (300 mg) saturates these proteins, leaving enough free drug to produce bactericidal effects on *P. aeruginosa*. In addition, pharmacokinetic analyses of inhaled tobramycin indicate that local concentrations of 25 times the minimum inhibitory concentration (i.e.,  $25 \times 4 \mu\text{g/mL}$ ) are required to kill *P. aeruginosa*.<sup>8</sup> At a total dose of 300 mg, sufficient sputum concentrations are achieved to produce a bactericidal effect in 90% of patients.<sup>9</sup> Thus, there seems to be a pharmaceutical, pharmacokinetic, and pharmacodynamic rationale for administering 300 mg of the drug.

With regard to clinical efficacy, there is high-quality evidence to support the use of tobramycin solution for inhalation. In a placebo-controlled trial, intermittent

tobramycin solution for inhalation (300 mg bid for 28 days on, 28 days off) yielded significant improvements (10% over baseline) in forced expiratory volume in the first second ( $\text{FEV}_1$ ) at 20 weeks.<sup>10</sup> In an extension of this study,  $\text{FEV}_1$  continued to improve until the end of the 92-week study period.<sup>11</sup> This trial, which represents the majority of available evidence, also showed that use of tobramycin solution for inhalation significantly reduced the density of *P. aeruginosa* in the sputum (by 0.8  $\log_{10}$  colony-forming units), reduced admissions to hospital (by 26%), and decreased the need for IV antibiotics (by 36%).<sup>10</sup> Moreover, a recent study indicated that tobramycin solution for inhalation (300 mg), when used consistently, was associated with an absolute mortality reduction of 2.8% at 5 years and 5.1% at 10 years relative to suboptimal use.<sup>12</sup> Finally, the safety of inhaled tobramycin 300 mg bid has been demonstrated, with voice alterations and transient tinnitus as the predominant adverse effects reported.<sup>9</sup>

Given all of the evidence supporting the use of tobramycin solution for inhalation at a dose of 300 mg bid, why aren't we using this regimen consistently? The main reason appears to be economic. For patients with cystic fibrosis, medication costs can be high, and many rely on government assistance. Tobramycin solution for inhalation is expensive, and as a result, coverage by provincial drug plans is variable, with some preferentially covering tobramycin for injection instead. Practitioners are forced to set aside the principles of evidence-based medicine and use the injectable formulation by inhalation at a dose (160 mg) that is not supported by the literature. In addition to considerations related to provincial drug coverage, another reason may be the time required to nebulize 300 mg of tobramycin for injection (total volume 7.5 mL), which would be prohibitively long compared with nebulization of 300 mg of tobramycin solution for inhalation (total volume 5 mL). This difference in volume might seem small, but not if consideration is given to the multiple time-intensive treatments that patients with cystic fibrosis must complete daily. We should try to improve adherence, not by selecting a regimen for which there is no evidence, but by selecting an available regimen that is evidence-based (even if it is expensive).

In this era of antimicrobial stewardship, we pharmacists have a better understanding of the implications of inappropriate dosing of antibiotics. Given the lack of published evidence to support the efficacy of tobramycin 160 mg bid, we may need to consider that evidence-based therapy for which adherence is more likely (i.e., tobramycin solution for inhalation) is simply the cost of good health care. Moreover, there is also the question of whether, by using 160 mg bid, we are in fact inadequately treating our patients and encouraging the establishment of resistant organisms in patients' airways. If we don't advocate on behalf of our patients for the reimbursement of evidence-based

therapies, we may get the answer to this question sooner rather than later, possibly at the expense of patient outcomes.

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## Collaboration: A Key Ingredient for Experiential Training

We enjoyed reading "Experiential Training for Pharmacy Students: Time for a New Approach", by Hall and others.<sup>1</sup> We applaud the authors for discussing this important topic and proposing suggestions for the pharmacist workforce to consider when working with faculties regarding experiential training.

In our experience, and as indicated in the literature, students are already providing value to patients during their experiential training,<sup>2</sup> but we acknowledge that there are opportunities to ensure that this occurs more consistently.

Hall and others<sup>1</sup> raised 2 concepts that we would like to specifically highlight. The first is the necessity of increasing early exposure to practice experiences. As faculties of pharmacy across Canada progress toward the entry-level PharmD, which requires a minimum of 40 weeks of experiential training, the opportunity now exists to design and implement experiential programs of sufficient *quantity* to address some of the concerns posed by Hall and others.<sup>1</sup> Such programs will include appropriate experience to support graduated independence for patient care from early years to the final year, consistent with the "medical model".<sup>3</sup> At the same time, ensuring *quality* of experience is a responsibility for both faculties and practitioner preceptors. Although some early-year experiential rotations may be partially designed for observation or exposure, baccalaureate senior-year rotations across Canada all include expectations of students' active participation on care teams and demonstration of their ability to provide pharmaceutical care. Preceptors should, if not already doing so, be requiring students to accept increased responsibility and accountability for the patient care they provide.

The second concept relates to supervision of students and how preceptors can provide such supervision in a meaningful way without feeling overloaded. Experiential education translates into a learning experience when actions are reflected upon and debriefed through discussion with a preceptor. Preceptors need to challenge their students, provide ongoing constructive feedback, and encourage self-directed learning. These aspects are critical to applying what is learned to new and more complex scenarios. As noted by the most recent Hospital Pharmacy in Canada report,<sup>4</sup> the biggest challenge associated with delivering experiential education is the associated workload. Preceptors must plan ahead for a rotation and anticipate whether they need to adapt their practice routine and schedule to create a supportive learning environment. An orientation during the first 72 hours is essential. An introduction to the work environment should be provided, along with discussion of previous learner experiences and the preceptor's expectations of the student. This will allow the preceptor to assign appropriate patient care responsibilities with limited supervision. The preceptor's investment of time into the student's development in the early phase of a rotation will usually lead to greater provision of care than if the preceptor were practising alone.<sup>5,6</sup> As noted by Hall and others,<sup>1</sup> additional mechanisms for increasing provision of patient care with a neutral effect on preceptor workload include peer-assisted learning<sup>7</sup> (i.e., multiple students with the same preceptor, with learning and problem-solving occurring among the students, before the preceptor becomes involved) and the pyramidal (medical) model<sup>8</sup> (i.e., attending pharmacist, resident, and senior and junior students creating a team). It was encouraging to note that a pyramidal model for learning is already being used by 28% of respondents to the Hospital Pharmacy in Canada