Potential consequences of essential drug shortages in Canada: Brain abscess due to *Nocardia farcinica* associated with dapsone prophylaxis for *Pneumocystis jirovecii* pneumonia

Terry C Wuerz MD FRCPC DTMH[1,2], Eric J Bow MD MSc D Bacteriol FRCPC[1,2,3], Matthew D Seftel MD MPH FRCPC MRCP[3]

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In 2012, Canadian pharmacies experienced a shortage of trimethoprim-sulfamethoxazole tablets. Drug shortages may result in unintended clinical consequences such as infection with pathogens against which the alternative medication is ineffective. This is highlighted in the present article, which describes a case of brain abscess due to *Nocardia* species that developed while receiving dapsone as an alternative for prophylaxis against *Pneumocystis jirovecii* pneumonia in a highly immune-suppressed patient. Clinicians should be cognizant of these issues when prescribing alternative agents.

Key Words: *Drug shortage;* Nocardia, *PCP prophylaxis;* Pneumocystis jirovecii*; Trimethoprim-sulfamethoxazole*

Les conséquences potentielles des pénuries de médicaments essentiels au Canada : un abcès cérébral causé par une *Nocardia farcinica* associée à une prophylaxie à la dapsone contre une pneumonie à *Pneumocystis jirovecii*

En 2012, les pharmacies canadiennes ont subi une pénurie de comprimés de triméthoprim-sulfaméthoxazole. Les pénuries de médicaments peuvent avoir des conséquences non intentionnelles, telles qu'une infection par des pathogènes contre lesquels le médicament de remplacement n'a pas d'effets. C'est ce qu'on souligne dans le présent article, qui décrit un cas d'abcès cérébral attribuable à une espèce de *Nocardia* qui s'est manifesté pendant l'administration de dapsone en prophylaxie de remplacement contre une pneumonie à *Pneumocystis jirovecii* chez un patient très immunodéprimé. Les cliniciens devraient connaître ces enjeux lorsqu'ils prescrivent des médicaments de remplacement.

Trimethoprim-sulfamethoxasole (TMP-SMX) is a commonly prescribed antimicrobial agent. It is indicated for prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) in patients with HIV and low CD4 T lymphocyte cell counts, as well as in patients receiving significant immune suppressive medications. The use of TMP-SMX is associated with a dramatic reduction in the risk of PCP (1). Although less well studied, infection with several other microbial pathogens is likely to be prevented by the use of TMP-SMX in these patients, including *Nocardia* species.

Beginning in May 2012, Canadian pharmacies experienced a shortage of TMP-SMX tablets. We present a case of brain abscess due to *Nocardia* species that developed while receiving dapsone as an alternative for prophylaxis against PCP in a highly immune-suppressed patient, and highlight the issues relating to use of drugs other than TMP-SMX in high-risk individuals.

CASE PRESENTATION

A 54-year-old man with chronic lymphocytic leukemia experienced an incomplete response to several courses of combination chemo-immunotherapy. His disease was determined to be high risk on the basis of his poor treatment response and his relatively young age. A 10/10 human leukocyte antigen-matched, related, allogeneic peripheral stem cell transplant (SCT) was performed following a myeloablative conditioning regimen. After weaning of his immunosuppressive regimen, he developed chronic graft-versus-host disease (GVHD) involving the skin, mouth and lungs in the 12 to 18 months following SCT. He was placed back on immunosuppression with mycophenolate mofetil, sirolimus, 1 mg/kg daily prednisone and topical tacrolimus cream. He had also been initiated on extracorporeal photopheresis. Prophylactic antimicrobials consisted of dapsone 100 mg three times per week and penicillin V 500 mg/day.

He presented 20 months after transplantation with a new fever of 38.8°C, and was noted to have a headache of mild to moderate intensity as well as photophobia. He appeared otherwise well, with normal vital signs, mental status and neurological examinations, and no evidence of meningismus. His peripheral white blood cell count was 13.3×10^9/L with a left shift and toxic granulation. A lumbar puncture performed to investigate the headache syndrome revealed abnormal cerebrospinal fluid (CSF) with a leukocytosis and neutrophilic pleocytosis (white blood cell count 6.750×10^9/L with 84% neutrophils, 5% lymphocytes and 11% monocytes), hypoglycorrachia (CSF glucose 1.5 µmol/L and serum glucose 5.6 µmol/L), and elevated protein of 3.52 g/L. A CSF Gram stain revealed no organisms, and a cryptococcal antigen test performed on the CSF was negative. Empirical therapy for a bacterial meningitis syndrome with vancomycin, ceftriaxone and ampicillin was associated with clinical improvement within 36 h.

Magnetic resonance imaging of the brain, six days after initiation of the antimicrobial agents, revealed a 5 mm ring-enhancing lesion in the right frontal lobe in the corpus callosum, immediately adjacent to the lateral ventricle (Figure 1). A thin, branching Gram-positive rod was isolated from the CSF culture, and ultimately identified by polymerase chain reaction 16s DNA sequencing as *Nocardia farcinica/Nocardia otitisdiscaviarum*, which demonstrated in vitro susceptibility to TMP-SMX. It was presumed that his clinical presentation was

[1]*Department of Internal Medicine, Section of Infectious Diseases;* [2]*Department of Medical Microbiology;* [3]*Department of Internal Medicine, Section of Haematology/Oncology, University of Manitoba, Winnipeg, Manitoba*

Correspondence: Dr Terry Wuerz, Department of Internal Medicine, University of Manitoba, 543 – 745 Bannatyne Avenue, Winnipeg, Manitoba R3E 0J9. Telephone 204-995-0063, fax 204-786-0196, e-mail terry.wuerz@gmail.com

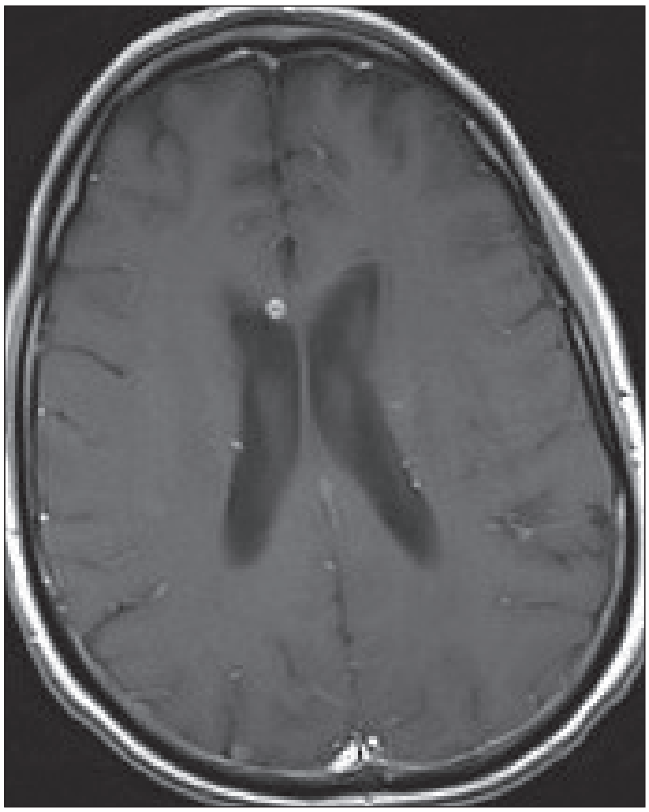

Figure 1) *T1 postgadolinium-enhanced magnetic resonance image of the brain*

related to cerebral *Nocardia* abscess with intraventricular rupture and subsequent meningeal reaction. The antimicrobial regimen was substituted with high-dose TMP-SMX oral suspension due to a national shortage of TMP-SMX tablets. Follow-up magnetic resonance imaging of the brain at an interval of six weeks demonstrated improvement in the size of the ring-enhancing lesion. A treatment duration of 12 months was planned.

DISCUSSION

In May 2012, the supply chain of oral TMP-SMX tablets was threatened by back-ordering of its two major manufacturers in Canada, Apotex and Teva. We contacted both companies, but the cause of the back-order was not made available to us. Drug shortages are not uncommon in developed countries such as Canada; they may be due to unanticipated demand, shortage of a single-source pharmaceutical ingredient, manufacturing errors or product discontinuation (2). Drug shortages in the United States have tripled in recent years for a variety of reasons (2) and are likely to become more common in the future.

The effects of drug shortages on clinical care should be anticipated, planned for and, when possible, avoided. There are many stakeholders responsible for an effective national drug supply, including individual clinicians, pharmacies, pharmaceutical companies and governmental organizations. Canada has been criticized for not doing enough to anticipate and mitigate the impact of drug shortages (3). As an initial strategy, steps toward the creation of a national mandatory reporting system for anticipated drug shortages should be undertaken. In the meantime, clinicians must develop contingency plans for interruptions in medication supply. Furthermore, it is important to consider the clinical consequences of specific drug shortages, such as TMP-SMX, on specific clinical scenarios such as PCP prophylaxis.

Nocardia species are Gram-positive aerobic branching bacilli, ubiquitous in soil and decaying plant matter. It is transmitted by inhalation or direct skin inoculation, and can cause localized or disseminated disease (including brain abscess) in humans. Immunosuppression, especially impairment of cell-mediated immunity, is the main risk factor for disease (4,5). The epidemiology of *Nocardia* infection in specific populations is not well studied. A large single-centre registry analysis determined an overall infection rate of 0.6% in solid organ transplant recipients (5); infection rates in SCT recipients are likely to be similar. A recent microbiological survey from Quebec (6) showed an increase in the total number of new clinical *Nocardia* isolates from 1997 to 2008. The increasing frequency of *Nocardia* infection is likely due, at least in part, to increasing immunosuppression, including solid and hematopoietic transplantation.

BOX 1
Pathogens proven or likely to be prevented using trimethoprim-sulfamethoxazole

Bacteria
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Listeria monocytogenes*
- *Haemophilus influenzae*
- *Legionella pneumophila*
- *Nocardia* species

Protozoa
- *Toxoplasma gondii*
- *Plasmodium species*

Fungi
- *Pneumocystis jirovecii*

Prophylaxis against PCP is recommended by the Canadian Blood and Marrow Transplant Group, the Infectious Disease Society of America and other international societies (7) for patients receiving an allogeneic SCT for six months post-transplant and until patients have completed all immunosuppressive medications. Similar recommendations have been made for PCP prophylaxis in solid organ transplantation (8). Ongoing indications for immunosuppression, such as GVHD, often necessitate a longer duration of PCP prophylaxis. TMP-SMX is the preferred agent, due to superior efficacy, compared with the alternatives dapsone, atovaquone and aerosolized pentamidine (1,7,8).

In addition to its established efficacy in prophylaxis of PCP, TMP-SMX has antimicrobial activity against other pathogens for which transplant recipients are at risk. *Nocardia* species are highly susceptible to TMP-SMX. Infection with *Nocardia* species is uncommon, and the effect of prophylaxis on their incidence has never been formally studied in any patient population. Other pathogens that are susceptible to TMP-SMX include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Haemophilus influenzae* and *Legionella pneumophila*. Collectively, these bacteria may represent a significant burden of infectious disease in the post-transplant setting.

The safety and utility of TMP-SMX for the prevention of infectious diseases other than PCP in immunocompromised patients is established. In a randomized controlled trial, TMP-SMX has been shown to prevent urinary tract and bloodstream infection in the early postrenal transplant setting (9). TMP-SMX is more effective in preventing central nervous system reactivation of *Toxoplasma gondii*, compared with aerosolized pentamidine, in persons with HIV (10); its use is also recommended in the post-transplant population for this purpose (7,8). Prophylaxis using agents other than TMP-SMX, therefore, is likely to increase the risk of infection due to a number of important pathogens, in addition to PCP. Infectious diseases proven or likely to be reduced by TMP-SMX are presented in Box 1.

With a few exceptions, alternative agents for the prophylaxis of PCP have little or no activity against many of the pathogens listed in Box 1 and could be expected to have little effect on their prevention. Aerosolized pentamadine does not penetrate the central nervous system, and its use in prophylaxis would not be expected to affect the frequency of pathogens other than PCP (7). Atovaquone is highly active against protozoal infections including *Plasmodium* species (ie, marketed

in combination with proguanil as Malarone [GlaxoSmithKline, USA]) as well as against *T gondii*. However, it has not been adequately studied for the purposes of *T gondii* prophylaxis (7). Dapsone, a sulphone antibiotic, has some activity against *T gondii* (7), *Plasmodium* and *Nocardia* species (3). Generally, dapsone must be combined with a dihydrofolate reductase inhibitor, such as pyrimethamine, to obtain clinical potency against these pathogens. This combination may result in significant bone marrow toxicity including irreversible agranulocytosis. Its use alone in prophylaxis against *T gondii* is also not well studied (7).

In summary, with the unavailability of TMP-SMX tablets, PCP prophylaxis with dapsone was associated with a breakthrough *Nocardia* infection of the central nervous system in this immunosuppressed SCT recipient. In this instance, TMP-SMX oral suspension, a viable alternative, remained available throughout the tablet shortage but was not considered. Prophylaxis using an alternative to TMP-SMX results in unreliable activity and unproven clinical utility against a wide spectrum of clinically relevant infectious pathogens. Strategies to mitigate these risks are also unproven. In patients at high risk for reactivation for toxoplasmosis, including SCT patients within the first six months after transplant or with steroid-refractory GVHD, additional use of clarithromycin or, alternatively, pyrimethamine plus leucovorin is appropriate (6). The incremental value of adding agents for primary prophylaxis of other bacterial infections, including *Nocardia* and *Listeria*, is unknown, and is not recommended at the present time (7,8).

As drug shortages become more common, the Canadian shortage of TMP-SMX raises important considerations for clinicians, who may be forced to choose an alternative drug. Drug shortages may cause unintended consequences for the patient, thereby adding to the complexity of care and increasing costs to the health care system. As illustrated in the present report, *Nocardia* and other infections are more likely to occur in transplant recipients who use PCP prophylactic agents other than TMP-SMX. Clinicians should be aware of the potential gaps in antimicrobial activity afforded by the use of these other agents.

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