

## Economic Barriers in the Treatment of *Clostridium difficile* Infection With Oral Vancomycin

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Vancomycin is an increasingly important option for the treatment of *Clostridium difficile* infection, but economic barriers to its use remain significant in the outpatient setting. Generic vancomycin capsules are still inexplicably expensive and not universally covered by insurers. This report highlights the potential adverse consequences of cost-related nonadherence to vancomycin therapy and the challenges that clinicians face when prescribing oral vancomycin.

**Keywords.** *Clostridium difficile*; pharmaceutical costs; vancomycin.

### CLINICAL VIGNETTE

A 56-year-old woman was hospitalized with recurrent *Clostridium difficile* infection (CDI), after 2 previous CDI episodes treated with metronidazole. She received oral vancomycin in the hospital and was discharged with a prescription for vancomycin capsules, assured by the case manager that the capsules would be covered by her prescription insurance. However, when the patient presented to the pharmacy post-discharge, she was informed that the prescription cost exceeded \$1000. She returned home while awaiting prior authorization request approval from her insurance provider, and she ultimately required readmission for incompletely treated CDI after 3 days without medication.

### BACKGROUND

The role of vancomycin in CDI treatment is evolving, with data suggesting higher success rates versus metronidazole regardless of severity [1]. Although economic discussions surrounding CDI pharmacotherapy often focus on fidaxomicin, financial

barriers to vancomycin access remain substantial and potentially unrecognized [2, 3]. The persistently high acquisition cost of generic vancomycin capsules and heterogeneous insurance reimbursement policies demand consideration in the selection of CDI pharmacotherapy.

### COST OF ORAL VANCOMYCIN

Vancomycin capsules were approved for treatment of CDI in 1986, and generic capsules became available from several manufacturers in 2012. In theory, the price of generic vancomycin capsules should have decreased dramatically compared with the branded price due to market competition [4]. The exceptions to this rule in recent years have included single-source generic agents, such as isoproterenol and nitroprusside, or those indicated for less common diseases, such as albendazole and pyrimethamine [5]. The US Food and Drug Administration (FDA) approval process for generic vancomycin capsules also favored a less costly development process, because manufacturers were only required to demonstrate bioequivalence to the branded capsule by in vitro dissolution studies rather than a human clinical trial [6]. Despite this, the initial generic cost of vancomycin after patent expiration was high and it has remained so ever since. One potential influence on the stability of this elevated price is the relative absence of generic manufacturer Abbreviated New Drug Applications (ANDAs) after the initial generics were approved. Four of the 5 approved generic manufacturers of vancomycin capsules received their approval within a 3-month period in 2012; the fifth became approved in January 2015 [7]. One conjecture may be that satisfaction with market share among the 4 initial generic companies translated into less competition than would be seen if manufacturers were entering the market in subsequent years. Currently, the average market share of vancomycin capsules, a market that exceeded \$100 million in 2015, is predominantly captured by one of the original generic companies (57%), with only 15% provided by the newest generic ANDA holder [8, 9].

Understanding medication costs in the United States is challenging because there is no gold standard representation of the true price. In published cost-effectiveness studies of oral vancomycin in the United States, the per-dose cost varies from \$5 to \$33 [2, 10]. Although it almost uniformly overestimates true acquisition costs, average wholesale price (AWP) is the only published reference that has been available for several years as a means of comparing vancomycin costs over time (Table 1). The AWP for generic vancomycin capsules has not changed since the value set in 2011–2012. The Wholesale Acquisition Cost, another cost metric that varies by manufacturer, reflects that 125-mg capsule rates range from \$12.5/capsule for the newest

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**Table 1. Oral Vancomycin Average Wholesale Price, 2010–2016 in US Dollars (per Dose) [11, 18, 19]**

Dosage Form	2010	2012	2014	2016
125 mg capsules, generic	Not available	31.3		
125 mg capsules, brand (Vancocin)	24.3	34.8	52.5	66.1
250 mg capsules, generic	Not available	57.7		
250 mg capsules, brand (Vancocin)	44.8	64.2	96.8	121.8
Compounded oral vancomycin solution from compounding kit (50 mg/mL)	Not available	Not available	Not available	1.0 <sup>a</sup>

<sup>a</sup>Dose for oral solution 2.5 mL = 125 mg.

generic company to approximately \$25/capsule for the original generic manufacturers [11]. The true acquisition costs to patients and the influence of competition from generic manufacturers thus depends on contracts, discounts for nonprofit organizations, competition, supply chain disruptions, and overhead costs. Despite this variability, our clinical experience has been that cash prescription prices for vancomycin capsules typically surpass several hundred dollars and often exceed \$1000.00 for a standard treatment course [12]. The comparatively lower cost of vancomycin capsules in other countries, such as the \$207 treatment courses cited by Canadian health formularies for a 10-day supply of 125-mg capsules, argues against the presence of any particular manufacturing or production expense that would be influencing costs [13].

As a cost-containment measure, pharmacies often compound an oral solution from intravenous vancomycin or compounding kits for patients who require oral vancomycin [14]. Although this oral solution is much less expensive than a comparable prescription for vancomycin capsules, the appropriate role of the solution for patients who could otherwise take capsules is controversial. In addition, the compounded solution is often not included in insurance formularies or major pricing compendia because it is not considered an FDA-approved medication. This omission renders prescription insurance coverage and pharmacy billing of oral vancomycin solution exceedingly challenging. The availability of vancomycin oral suspension for reconstitution, currently in development, may represent a future option for prescribers looking for a less expensive and FDA-approved vancomycin formulation.

### ORAL VANCOMYCIN COVERAGE BY PRESCRIPTION INSURANCE COMPANIES

Before the FDA approval of generic vancomycin capsules, Studemeister [15] published an editorial that criticized the lack of prescription insurance coverage for oral vancomycin, calling it “the elephant in the room”. In the 5 years since the editorial’s publication, little progress has been made in terms of expanding or standardizing oral vancomycin insurance coverage policies. Attempts to summarize coverage in a geographic area are challenging given the number of available plans and lack of publicly available formulary information. As an example, Illinois Medicaid programs classify generic vancomycin capsules as a

formulary agent, but many Medicare Part D prescription programs categorize vancomycin as a specialty tier medication that may or may not require a prior authorization for payment. Formulary status among commercial insurance plans varies from the lowest to the highest copay tiers.

### DISCUSSION

The clinical vignette illustrates the challenges in anticipating vancomycin cost in the outpatient clinic, which requires knowledge of the patient’s prescription insurance policy, its formulary, prior authorization requirements, and the balance of any annual deductible. The prescription policy is invariably distinct from the insurance covering the office visit or hospitalization, a source of confusion for both patients and healthcare providers. The vignette also highlights the consequences of failing to fill vancomycin in this setting; similar cases of CDI relapse related to the prohibitively high cost of vancomycin have been reported [3].

Our University CDI referral clinic has witnessed dozens of examples of patients who have been unable to obtain vancomycin due to financial barriers, many of whom have experienced recurrences or hospitalizations. Oral vancomycin is prescribed for approximately 12 patients per month in our clinic, and this volume requires our clinic nurses to spend extensive time and resources submitting prior authorization appeals and contacting insurance companies. The implications of the “specialty tier” Medicare Part D designation is that many of our patients over 65 years of age struggle to afford the copay for vancomycin capsules, because they are required to pay a percentage of the substantial overall cost. Compounded vancomycin solution has in some instances been prescribed as a lower cost alternative, but even with electronic decision support it is difficult to predict at the time of prescribing whether capsules or solution would be the better financial option.

The vancomycin cost problem is unique for several reasons. Although prescription prices in the United States have received recent attention in both the medical literature and the lay press, generic medications such as vancomycin with a consistently high cost are typically not discussed in news outlets [4, 16]. Because it is not frequently mentioned in cost-centered media discussions, nonspecialist prescribers might be unaware of the financial implications. The recent Government

Accountability Office report on generic drugs under Medicare highlighted extraordinary price increases among generic drugs but did not address the issue of sustained high price generics [17]. Computerized electronic order entry systems may provide some formulary-related decision support, but these applications vary in accuracy and clinical appropriateness and may add to provider confusion. Tools that help patients afford other expensive medications, such as specialty pharmacy dispensing services or industry-sponsored patient assistance programs, do not exist for high-cost generic medications such as vancomycin. Most importantly, in contrast to expensive pharmacotherapy for chronic disease states, vancomycin is often time-sensitive to the degree that a dispensing delay of several days can lead to poor outcomes.

## CONCLUSIONS

Financial barriers complicate delivery of optimal care for patients with CDI, an infection with a rising prevalence in the United States and high associated morbidity. The problem stems from the persistently high cost of the generic capsules as well as inconsistent coverage policies among prescription insurance formularies. Providers often do not know at the time of writing the prescription whether it will require authorization or have a prohibitively high copay, potentially resulting in delayed, incomplete treatment, or no treatment at all. Until insurance coverage of oral vancomycin products is expanded, clinicians are urged to be proactive in determining the financial impact to patients and in submitting authorizations or switching to lower-cost alternatives before patients leave the point of care. Given the increasing role of vancomycin in the management of CDI, efforts should be made to lower the costs and improve access to this antibiotic. Given the cost of nonadherence and readmissions due to recurrent CDI, this is a disease state in which we cannot afford to fail.

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