The Risks of Reflexive Refilling

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ABSTRACT

Introduction: The electronic health record and electronic prescribing have transformed the practice of medicine. Both have led to improved efficacy and safety in medication management. However, dangers may arise when electronic prescription requests are filled by default and when electronic health record medication lists are presumed accurate. In this case, our patient underwent 2 days of inpatient evaluation before a thorough medication reconciliation revealed that his symptoms had likely resulted from a medication that had been refilled reflexively.

Case Presentation: A 69-year-old man presented with worsening weakness, weight loss, decreased appetite, and nonbloody diarrhea. Imaging revealed a large right pleural effusion and a nonspecific colitis. Lab workup revealed significant bicytopenia, hypogammaglobulinemia, and hypolipidemia. Initial evaluation and diagnoses were focused toward causes of malnutrition and malabsorption. However, on hospital day 2, a pharmacist discovered that the patient had been taking long-term oral linezolid for unclear reasons. With cessation of linezolid, the patient's myriad symptoms resolved and all lab values progressively normalized.

Discussion: The side effects of linezolid have been well documented and include reversible myelosuppression and gastrointestinal symptoms. However, medication reconciliation was imperative in diagnosing and treating our patient. Further, reflexive refilling of this patient's medication likely explains why he was taking linezolid for such a long period of time, as other forms of automation bias are known to introduce errors in electronic prescribing.

Conclusion: This case calls attention to the importance of medication reconciliation, the danger of overreliance on electronic health record medication lists, and the pitfalls in not maintaining vigilance with electronic prescribing. It also highlights the necessity of patient and caregiver education regarding their medications.

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INTRODUCTION

The electronic health record (EHR) and electronic prescribing (e-prescribing) have transformed the practice of medicine. Both have led to improved efficacy and safety in medication management. However, dangers may arise when electronic prescription requests are filled by default and when EHR medication lists are presumed accurate.

We report the case of a patient who underwent 2 days of inpatient evaluation before a thorough medication reconciliation revealed that his symptoms had likely resulted from a medication that had been refilled reflexively.

CASE PRESENTATION

A 69-year-old man with hypertension, diabetes mellitus, and previous below-the-knee amputation presented to the emergency department (ED) for worsening weakness, hair loss, decreased appetite, and watery, nonbloody diarrhea. His symptoms began insidiously and developed over several weeks. His weakness was characterized by difficulty in wheelchair transfers and several falls. He had no fevers but had lost 25 pounds since his last recorded weight 3 months earlier. The remainder of his review of systems was negative. His vital signs were normal, and his physical examination was notable only for pallor and alopecia. In the ED, he had a hemoglobin of 5.0 g/dL and a platelet count of 72×10^6/uL compared to values of 8.7 g/dL and 246×10^6/uL, respectively, 5 months earlier. Additionally, computed tomography (CT) of the abdomen revealed a large right pleural effusion

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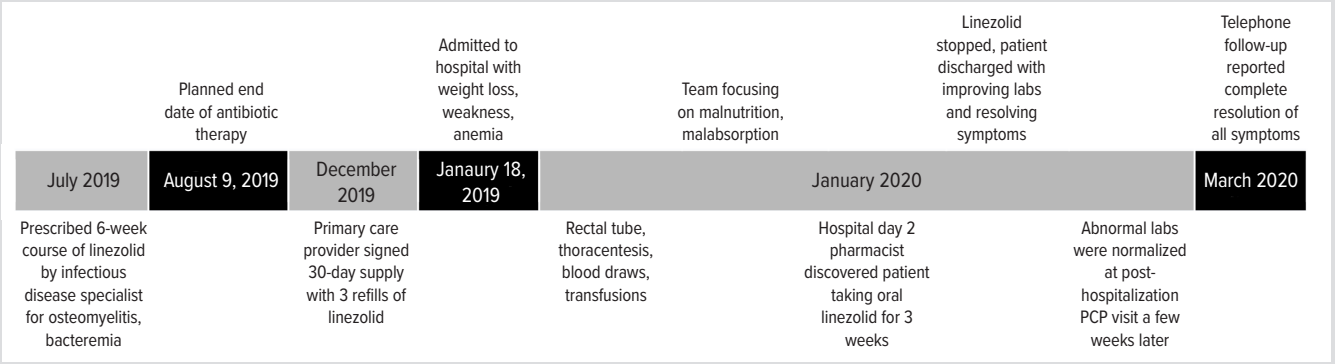
Figure. Timeline of Linezolid Treatment



and nonspecific colitis. He received 2 units of packed red cells and was admitted to the medicine ward for further management and evaluation. Workup of his bicytopenia revealed normal iron stores but profound reticulocytopenia (0.05 10^6/uL). He underwent thoracentesis, which revealed transudative fluid. His diarrhea was negative for common viruses, bacteria, and parasites. His albumin was 3.6 g/dL, total protein was 5.5 g/dL with hypogammaglobulinemia, and his low-density lipoprotein cholesterol (LDL-C) was less than 4 g/dL. Thus, our team began to focus evaluation toward malnutrition and malabsorption.

While the admitting physicians performed a cursory medication reconciliation based on the patient's most recent electronic medication list, on hospital day 2, an inpatient pharmacist performed a more thorough review of the patient's outpatient medications. The pharmacist used multiple data sources, including the patient's recollection, his wife's report of medications physically in their possession at home, a prescription adjudication database with dispensations, and both the local EHR and linked EHRs in other health care organizations. Upon completion of this thorough reconciliation, the pharmacist discovered that the patient had been taking oral linezolid for 3 weeks. Although linezolid had not appeared on any of the patient's electronic medication lists, we verified the prescription had been electronically signed by his primary care provider (PCP) for a 30-day supply with 3 refills. A timeline of the patient's linezolid prescriptions and symptoms can be viewed in the Figure. Neither the patient nor his wife could provide a reason for the prescription, and we found no clinician documentation justifying this refill. The patient's PCP was contacted via telephone in an attempt to clarify the prescription. Unfortunately, the PCP did not recall why the antibiotic was restarted.

In reviewing the EHR, we discovered that the patient had received a 6-week course of linezolid 6 months prior for osteomyelitis and Staphylococcus aureus bacteremia. As we could find no rationale for the current prescription, we surmised that an errant electronic refill was generated by his pharmacy and inattentively refilled in his PCP's office.

With cessation of linezolid, the patient's reticulocyte count and platelet count quickly normalized. In a post-hospitalization primary care visit, his hemoglobin had risen to 10.7 mg/dL, his LDL-C was 30 mg/dL, and his diarrhea had subsided. In a telephone follow-up 3 months later, he reported complete resolution of all his symptoms. Approximately 9 months after hospitalization, his hemoglobin had completely normalized and his weight had returned to his previous baseline.

DISCUSSION

Linezolid is an antibacterial agent with broad-spectrum activity against gram-positive organisms. Its side effects include reversible myelosuppression. While thrombocytopenia is more common, anemia may also complicate long-term linezolid use.[1] Linezolid exhibits its therapeutic effects by inhibiting protein synthesis via blockade of the bacterial ribosome 50S subunit. However, this activity may affect human mitochondrial protein synthesis and thus may contribute to broader mitochondrial toxicity across multiple tissue types.[2] Given these wide-ranging effects, we speculate that the patient's bicytopenia, alopecia, hypolipoproteinemia, and presumed malabsorptive diarrhea all related to prolonged linezolid toxicity.

This case calls attention to the importance of medication reconciliation and the perils of over-reliance on EHR-based medication lists and e-prescribing. The primary goals of electronic medication lists and e-prescribing are to improve the quality, clarity, and safety of medication prescriptions. E-prescribing has led to fewer adverse drug events and errors, and it has improved the efficiency of the prescribing process.[3] Further, it saves administrative costs and increases patient adherence.[3] While e-prescribing has improved overall medication safety, errors may still occur if electronic medication lists are not routinely reconciled[4] or if EHR warnings are ignored due to alert fatigue.[3]

The advent of e-prescribing gave rise to clinical decision support (CDS) systems that alert prescribers to potential errors. However, while helpful, e-prescribing and associated CDS are prone to inaccuracies. For example, automation bias may occur when clinicians excessively rely on CDS; this bias is formally

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defined as "the tendency to use automated cues [such as CDS alerts] as a heuristic replacement for vigilant information seeking and processing."[5] In one observational study, researchers examined how automation bias affected e-prescribing in simulated clinical scenarios and found that overreliance on CDS can lead clinicians to make both omission errors (ie, failing to notice mistakes unless notified by CDS software) and commission errors (ie, rotely complying with incorrect CDS suggestions). Specifically, when CDS provided incorrect information—either by failing to alert or creating a "false alarm" alert—prescribing errors increased by 86.6%.

Alert fatigue is a related byproduct of CDS and is described as a "mental state that is the result of too many alerts consuming time and mental energy."[6] In a review of CDS alerts, safety alerts were overridden in 49% to 96% of cases, with irrelevance and repeated information most often cited as reasons for overriding.[6] Other studies have shown that prescribers often disagree with CDS alerts, especially when the patient was already taking the medication or in the absence of a true contraindication.[5] Finally, another study that examined CDS alert fatigue found that clinicians were less likely to accept best practice reminders when the number of reminders and frequency of repeated reminders were higher.[7] Although we lack direct proof, we speculate that the ease and efficiency of e-prescribing, along with the known risk factors of automation bias and alert fatigue, may have contributed to reflexively refilling linezolid for our patient.[5-7]

While the goal of electronic medication lists is to improve safety and efficiency, they are often incorrect and outdated. Unfortunately, these inaccuracies are common, with a 2015 systematic review finding that from 20% to 87% (median 60%) of discharged patients had errors in their EHR medication lists. The most common medication list discrepancies are simply medication omissions. Importantly, this systematic review also found a correlation between the number of medication discrepancies and the total number of medications a patient was prescribed.[8]

Thus, authorities in medication safety have emphasized medication reconciliation—particularly at points of transition in care—as a solution to the wide reach of medication-related harm.[9-11] The World Health Organization (WHO) defines medication reconciliation as a formal process in which health care professionals and patients together ensure medication list accuracy at all care interfaces.[9] Steps in the medication reconciliation process, as outlined by the WHO, include (1) obtaining the best possible medication history, (2) confirming history accuracy, (3) reconciling the history with currently prescribed medications, and (4) supplying accurate information about the medications.[10] Further, the Joint Commission listed medication reconciliation as a national patient safety goal for 2020 and outlined a process that builds upon WHO recommendations. This process also includes defining the medication (including name, dose, route, frequency, and purpose), comparing the patient's medications to the medications that are ordered, and explaining to patients how to manage their medications.[11] The MATCH toolkit (Medications at Transitions and Clinical Handoffs) is a useful resource for practical implementation of medication reconciliation best practices.[12] Had our clinical pharmacist not manually reconciled the EHR medication list through meticulous tracking of medication dispensing data, we would have pursued a costly and unnecessary evaluation for malabsorption and malnutrition. Moreover, failure to discover and discontinue the patient's linezolid prescription could have led to recurrent symptoms after hospitalization when the patient resumed his home prescriptions.

Ostensibly, if frequent medication reconciliation by a clinical pharmacist were feasible in the outpatient setting, our patient may have been spared from hospitalization entirely. In one hospital-based multicenter quality improvement initiative, interventions that led to decreased rates of medication discrepancies included providing clear definitions of clinical roles and responsibilities in medication reconciliation and hiring dedicated staff (usually pharmacists) to perform medication reconciliation at discharge.[13] In fact, the literature largely supports pharmacist-led medication reconciliation as a safety mechanism. A systematic review found that adverse drug event-related hospital revisits and hospital readmissions were reduced after implementation of pharmacist-led medication reconciliation interventions at transitions of care.[14] In a separate review, pharmacist-led reconciliation interventions decreased the number of medication discrepancies and adverse drug events.[15]

This case also highlights the imperative to educate patients and caregivers on their medications. Patients' understanding of medication instructions and indications, empowerment, and self-efficacy with medication management all correlate with improved compliance.[16] By extension, such engagement should predictably reduce medication errors. Further, several studies and guidelines have highlighted the importance of patient and caregiver education regarding their medications when performing effective medication reconciliation.[11,15] While our patient's wife maintained his medication list, we discovered that both she and he had poor understanding of the medications' indications. Perhaps hospitalization could have been avoided if they had a clear understanding of why linezolid—an antibiotic that had been used to treat a systemic infection previously—was being represcribed. The case also calls attention to the broader issue of patient health literacy. Low health literacy is associated with poor health outcomes, including the abilities to correctly take medications and interpret medication labels.[17] Interventions to improve health literacy include using plain and nonmedical language in verbal and written communications, using visual aids and models, empowering patients to participate and manage their care, and providing support systems when necessary.[17]

Beginning in 2021, pharmacists in Wisconsin are no longer required to counsel patients on refilled prescriptions so long as

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the patient has taken the drug previously, the therapy has not changed, the patient does not request counsel, and the pharmacist does not deem it necessary.[18] While this may decrease workload for pharmacists, it may prove detrimental to patient safety and well-being. Certainly, our patient would have benefited from an earlier intervention and counseling from a pharmacist regarding his linezolid refill. However, since this case occurred in early 2020, he presumably did receive some counsel regarding the refill, which again highlights the importance of patient health literacy and medication reconciliation at multiple transitions of care. Ultimately it must be a combined effort on the part of physicians, pharmacists, and patients to ensure that medications are prescribed, managed, and taken safely and appropriately.

CONCLUSION

This case calls attention to the importance of medication reconciliation, the danger of overreliance on electronic health record medication lists, and the pitfalls in not maintaining vigilance with electronic prescribing. It also highlights the necessity of patient and caregiver education regarding their medications.

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REFERENCES

1. Gerson SL, Kaplan SL, Bruss JB, et al. Hematologic effects of linezolid: summary of clinical experience. *Antimicrob Agents Chemother.* 2002;46(8):2723-2726. doi:10.1128/AAC.46.8.2723-2726.2002

2. McKee EE, Ferguson M, Bentley AT, Marks TA. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. *Antimicrob Agents Chemother.* 2006;50(6):2042-2049. doi:10.1128/AAC.01411-05

3. Porterfield A, Engelbert K, Coustasse A. Electronic prescribing: improving the efficiency and accuracy of prescribing in the ambulatory care setting. *Perspect Health Inf Manag.* 2014;11(Spring):1g.

4. Nemeth LS, Wessell AM. Improving medication safety in primary care using electronic health records. *J Patient Saf.* 2010;6(4):238-243. doi:10.1097/pts.0b013e3181fe401f

5. Lyell D, Magrabi F, Raban MZ, et al. Automation bias in electronic prescribing. *BMC Med Inform Decis Mak*. 2017;17(1):28. doi:10.1186/s12911-017-0425-5

6. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc*. 2006;13(2):138-147. doi:10.1197/jamia.M1809

7. Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal R; HITEC Investigators. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak*. 2017;17(1):36. doi:10.1186/s12911-017-0430-8

8. Michaelsen MH, McCague P, Bradley CP, Sahm LJ. Medication reconciliation at discharge from hospital: a systematic review of the quantitative literature. *Pharmacy (Basel)*. 2015;3(2):53-71. doi:10.3390/pharmacy3020053

9. *Medication Safety in Transitions of Care.* World Health Organization; 2019.

10. *The High 5s Project – Standard Operating Protocol: Assuring Medication Accuracy at Transitions in Care: Medical Reconciliation*. World Health Organization; 2014.

11. National Patient Safety Goals Effective July 2020 for the Ambulatory Health Care Program. The Joint Commission. Published July 2020. Accessed January 4, 2021. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020/npsg_chapter_ahc_jul2020.pdf

12. Gleason KM, Brake H, Agramonte V, Perfetti C. Medications at Transitions and Clinical Handoffs (MATCH) toolkit for medication reconciliation. Agency for Healthcare Research and Quality Publication 11(12)-0059. August 2012. Accessed January 4, 2021. https://www.ahrq.gov/patient-safety/resources/match/index.html

13. Mixon AS, Kripalani S, Stein J, et al. An on-treatment analysis of the MARQUIS study: interventions to improve inpatient medication reconciliation. *J Hosp Med.* 2019;14(10):614-617. doi:10.12788/jhm.3308

14. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. *BMJ Open.* 2016;6(2):e010003. doi:10.1136/bmjopen-2015-010003

15. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. *Arch Intern Me*d. 2012;172(14):1057-1069. doi:10.1001/archinternmed.2012.2246

16. Náfrádi L, Nakamoto K, Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLoS One*. 2017;12(10):e0186458. doi:10.1371/journal.pone.0186458

17. Hersh L, Salzman B, Snyderman D. Health literacy in primary care practice. *Am Fam Physician*. 2015;92(2):118-124.

18. Wis. Admin. Code § Phar 7.08 (2021)

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