A trial of inpatient indication based prescribing during computerized order entry with medications commonly used off-label

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Summary

Background: Requiring indications for inpatient medication orders may improve the quality of prescribing and allow for easier placement of diagnoses on the problem list. Indications for inpatient medication orders are also required by some regulators.
Objective: This study assessed a clinical decision support (CDS) system designed to obtain indications and document problems during inpatient computerized physician order entry (CPOE) of medications frequently used off-label.
Methods: A convenience sample of three medications frequently used off-label were selected: the PPI lansoprazole; intravenous immune globulin, and recombinant Factor VIIa. Alerts triggered when a medication was ordered without an FDA approved indication in the problem list. The alerts prompted clinicians to enter either a labeled or off-label indication for the order. Chart review was used as the gold standard to assess the accuracy of clinician entered information.
Results: The PPI intervention generated 873 alerts during 60 days of operation; IVIG 55 alerts during alerts during 93 days; Factor VIIa 25 alerts during 175 days. Agreement between indications entered and chart review was 63% for PPI, 49% for IVIG, and 29% for Factor VIIa. The alerts for PPI, IVIG and Factor VIIa alerts produced accurate diagnoses for the problem list 9%, 16% and 24% respectively. Rates of off-label use measured by chart review were 87% for PPI, and 100% for IVIG and factor VIIa, which were higher than if measured using the ordering clinicians' indications.
Conclusion: This trial of indication-based prescribing using CDS and CPOE produced less than optimal accuracy of the indication data as well as a low yield of accurate problems placed on the problem list. These results demonstrate the challenge inherent in obtaining accurate indication information during prescribing and should raise concerns over potential mandates for indication based prescribing and motivate further study of appropriate mechanisms to obtain indications during CPOE.

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1. Background

Linking clinical indications with prescribed medicines should be useful in improving evidence-based and appropriate prescribing, and enhance comparative effectiveness research and patient safety. As of 2009, the Joint Commission required all medications on an inpatient formulary to be approved for particular indications and all medication orders to be compared to these indications [1]. Currently, indication is not a typical element of computerized physician order entry (CPOE) of medications and little research exists regarding mechanisms for acquiring indication at the point of ordering. The most widely used sources of coded information regarding diagnoses remains ICD9 codes available from billing records. Though required by the Joint Commission, and needed for the Health Information Technology for Economic and Clinical Health Act (HITECH) authorized incentive payments for meaningful use, problem lists, especially in electronic medical records (EMR) are often incomplete and seldom used [1-3]. Diagnoses in problem lists and billing code lists tend to be aggregated and/or coded inaccurately and offer an imperfect link to medication orders as many medications have multiple indications, many diagnoses do not receive medication therapy, and many diagnoses may be missing.

The use of medications in the ambulatory setting for indications that are not present on the official FDA label (off-label), has received greater attention in the literature in recent years. Recent studies have found that upwards of 20% of ambulatory prescriptions are issued for indications that are off-label and that a majority of those uses occur without substantial evidence [4]. The off-label use of prescription medications is legal and has been found in certain cases to be evidence-based, but also has the potential to be wasteful and even harmful [4]. Very little is known about the magnitude of off-label drug use in the inpatient setting outside of treatment of specific conditions, particularly cancer [5].

Recent growth in the use of EMR's and CPOE offers an opportunity to collect information regarding indications when a medication order or prescription is issued by a physician [6]. The development of EMR's has facilitated a variety of electronic based interventions to improve prescribing [7]. Examples include warnings for drug-drug interactions, encouraging of switching from IV to PO medications where appropriate, and linkages between drug use and lab values [8, 9].

Efforts to collect information on indication using EMR's and CPOE are less prevalent in the literature. However, a recent study explored the use of a CPOE intervention to add to the problem list when a medicine was prescribed and a related indication was not present [6]. This study demonstrated that among drugs selected to minimize physician burden by having relatively few associated indications, that the intervention was able to improve problem list documentation through the addition of relatively accurate diagnoses and had a high yield of problems placed per alert given.

2. Objectives

This study examined a clinical decision support (CDS) based CPOE alert mechanism for gathering data regarding medication order indications. Further, there was a specific focus on drugs frequently used off-label in the inpatient setting. The prevalence of off-label use for the three drug classes of interest (PPI, IVIG, and Factor VIIa) was also measured. The alerts were evaluated in terms of accuracy of the ordering clinician entered indication, placement of diagnoses on the problem list, and the indication data for labeled vs. off-labeled use and evidence vs. non-evidence based use.

3. Methods

This was a prospective observational pilot study conducted at an urban tertiary academic hospital that utilizes an EMR, CPOE and CDS [6, 11]. The majority of orders entered using CPOE were placed by house staff. A convenience sample of three medications were selected based on clinical interest and likelihood of off-label use from prior manual drug utilization reviews: the proton pump inhibitor (PPI), lansoprazole, the IVIG Flebogamma®, and the Factor VIIa, Novoseven®.

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We chose PPI's because they are known to be widely used off-label in high volumes of patients and patient are often sent home on a PPI based on off-label use [12]. We chose IVIG and Factor VIIa in part because they are very costly, but also because they were thought to be prescribed for a variety of off-label indications [13]. The PPI, IVIG and Factor VIIa interventions ran for 60, 93, and 175 days respectively. The PPI intervention was measured for 60 days and the other two alerts were run as long as possible given time constraints of the project.

3.1 Alert Development

For the selected drugs, alerts were designed to trigger a pop-up screen when physicians initiated a drug order using CPOE (▶Fig. 1a). To minimize physician burden, alerts were not triggered when appropriate indications/diagnoses were already listed in the electronic problem list. A list of these appropriate ICD-9 diagnoses can be obtained from W.G. if requested. The alerts requested clinicians to enter a labeled indication (plus one a priori known off-label use for Factor VIIa) which would then be automatically placed on the problem list. If they chose not to enter a first-screen indication, they were given the option of entering an off-label indication, a free text indication, or not entering any indication (▶Fig. 1b). Note that this second level of options was not available in the prior study noted above [6]. Free text indications and the off-label indications from the second screen (▶Fig. 1b) were not placed on the problem list.

3.2 Chart Review for indication

Expert chart review was used as the gold-standard for evaluating the actual indication. For the PPI, a random sample of 100 charts were reviewed. For Factor VIIa, and IVIG, all charts were reviewed. Two clinicians, either pharmacists or attending physicians, conducted a chart review to identify the actual indication for the medication order. Any disagreement was mediated by a third clinician blinded to the previously determined indications to break the tie.

3.3 Chart Review for continuation of lansoprazole

For lansoprazole, the only oral medication studied, charts were also reviewed to determine whether or not the patient was on a PPI at admission, whether the patient was discharged on a PPI, and, if so, was it lansoprazole.

3.4 Analysis

For each medication, the proportion of orders where the prescribing physician provided an indication was determined. This proportion is referred to as the *yield* of the alert. In addition, the proportion of orders where the indication provided by the prescribing physician matched the expert indication was determined. This proportion is referred to as the *accuracy* of the indication. Note that matching of the indication was determined by hand, case by case, not via a computer program or algorithm.

When a first-screen indication was provided, a problem was added to the problem list. The proportion of alerts which provided a new problem list addition is called the *problem list placement yield*. The problems added were compared to chart review to measure accuracy which is called *problem list accuracy*.

Statistical significance in differences in accuracy across drugs was examined via a simple logistic model. The model had an indicator for accuracy as the dependant variable and indicators for each drug as dependent variables using lansoprazole as the reference group.

Any indication provided by the ordering clinician, as well as the actual indication from the chart review, were analyzed to determine if they were FDA approved, off-label, and if off-label were they evidence based. Whether an indication was evidence-based, was categorized in a manner similar to Radley et al [4] using DrugDex [14]. DrugDex [14] assesses evidence by drug and indication and provides the following three assessments:

1. Efficacy (in four categories: "effective," "evidence favors efficacy," "evidence is inconclusive," and "ineffective");

2. Strength of recommendation in four categories:
   - "Class I-recommended,"
   - "Class IIa-recommended in most cases,"
   - "Class IIb-recommended in some cases," and
   - "Class III-not recommended;
3. Strength of evidence [in three graded categories:
   - "A," - good RCT evidence
   - "B," - less consistent RCT evidence) and
   - "C" - non-RCT forms of evidence).

An indication was deemed evidence-based if it met the following three criteria:
1. Efficacy was at least "evidence favors efficacy",
2. Strength of recommendation was at least IIa (recommended in most cases) and
3. Strength of evidence is at least Class B (data beyond case-series and expert opinion).

Note that the determination of off-label and evidence-based use was done based on labeling and evidence for any drug within the class of medications, for example, off-label and evidence-based for any PPI.

4. Results

The PPI, IVIG and Factor VIIa alerts ran for 60, 93 and 175 days respectively, and 873, 55, and 25 alerts were displayed to clinicians as shown in ▶Table 1. As expected, the majority of the orders were initiated by house staff, 93%. Others ordering included attendings, advanced practice nurses, physician assistants, and students. Overall agreement between the 2 reviewers was 85% for all indications. Hence, a third reviewer was used for 15% of the charts and in all of those the third reviewer agreed with one of the two prior reviewers. Substantial yields of indications were observed for the alerts; 95±2% for PPI, 75±6% for IVIG, and 96±3% for Factor VIIa (▶Table 1). Since only first-screen indications could produce placement of a diagnosis on the problem list, problem list placement yields were lower; 38±5% for PPI, 22±6% for IVIG, and 64±10% for Factor VIIa (▶ Table 1).

▶Table 2 shows the proportion of indications that were off-label and not evidence-based. Using our conservative definition, indication at the class level, the rate of non evidence-based use ranged from 77% (PPI) to 85.6% (IVIG) to 100% (Factor VIIa).

The accuracy of clinician placed indications is shown in ▶Table 3. Only modest accuracy for the alert-reported diagnoses was noted: 63% for PPI, 49% for IVIG and 29% for Factor VIIa, with the accuracy for PPI being statistically significantly greater than that of Factor VIIa (P = 0.004). The accuracy was also determined based on whether the actual indication was labeled or evidence-based. We found that physicians used free text versus the drop-down menu 5 times in the PPI sample, 3 times for IVIG, and 2 times for Factor VIIa. When free text was used, the accuracy was 100%, 66%, and 100% respectively.

A description of all the indications listed and their FDA approval status as well as evidence base is shown in ▶Table 4. The most common actual indication that was FDA approved or evidence-based were gastroesophageal reflux disease and idiopathic thrombocytopenic purpura for the PPI and IVIG respectively.

Of the sample of 100 PPI patients, 22% were not on a PPI at admission but were discharged on a PPI. Not surprisingly, the discharge PPI was most commonly lansoprazole (77%). The indication for inpatient PPI orders for these patients is shown in ▶Table 5. Taking the inpatient indication as the reason for a prescribed PPI at discharge, the PPI prescriptions at discharge were not for an FDA approved indication roughly 90% of the time.

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5. Discussion

The intervention we examined was robust in obtaining indications from the ordering clinicians. The yields varied between 75% and 96%. This is similar to that found in a previous study that examined medications with fewer indications [6]. The yield was far from optimal, but also likely high enough to be useful given the cost of the intervention. Further, the yield could be improved with mandatory fields in the CPOE ordering screens as well as other design optimization of the user interface.

On the other hand, the accuracy of the indications found here was lower than in the previous study [6]. The indications for Factor VIIa were correct less than a third of the time, while the best performing alert was that for lansoprazole with an accuracy of roughly two thirds. The prior study had accuracies in the range of 80% to 100%, depending on the medication. This discrepancy is likely due to the deliberate selection of medications with multiple on-label and off-label indications in the present study. The prior work deliberately selected medications with few and relatively unambiguous indications to maximize accuracy of diagnoses added to the problem list. Taken together, these data suggest that in terms of the accuracy of indications entered, one can expect variable success in promoting inpatient indication based prescribing. The degree of success is likely to depend upon the particular medication in question. As a consequence, mandates to require indication information may in some cases produce poor quality data, or at least require greatly improved user interfaces and logic to be successful.

As with many information gathering tools, there is a tradeoff between the quality of information and user burden. Time taken for the alerts may be justified when appropriate, but create nuisance when not appropriate. Nonetheless, the value of a connection between a medication order and it's indication has great potential in improving the use of medications over time by providing more detailed information for assessment and evidence generation. This type of data has the potential to improve knowledge regarding what works, when it works, and for whom.

For drugs being used off label, the link between prescriptions and indication is likely to be particularly valuable. For example, there could be interventions to suggest on label alternatives, or off label alternatives with a higher degree of evidence, if they have not already been tried. Further, if clinicians deem off label uses as the best option, it is useful to track the use for future evidence of the health improvement achieved. Note that our results serve to confirm, as many clinicians know well, that there is a substantial amount of off label ordering. As clinicians learn more about the function of medications, they naturally find indications for them that were not part of the initial clinical trials. Until strong evidence is gathered that changes the FDA indications, the new indication will not be added to the FDA label, and drug companies typically have little incentive to fund studies to expand the number of indications on the label. Stronger links in medical records between indications and prescriptions can serve to assist clinicians in learning about which treatments work for particular situations.

There is also a potentially useful role for this type of alert to augment the overall diagnostic data in the EMR. Though evidence remains very limited, and any such assessment was beyond the scope of the analyses conducted in this study, there is reason to believe that improved problem lists can assist generally in treatment selection, coordination of treatments for patients with multiple indications, and reduction of treatment errors. This may be accomplished in part by using CDS to leverage the information in the problem list to produce recommendations for improvement in the safety or efficiency of care. A useful area for future research would be to examine whether there is a link between accurate problem lists and improved quality of care.

Presently there is great emphasis on improving the quality of problem lists due to efforts to receiving "*meaningful use*" incentive dollars [2], as well as to ensure compliance with the joint commission standards [1]. This type of CDS, which can link problem list placement to the routine workflow of placing orders or order sets, and which is already being done at many institutions, should be investigated further.

Of particularly high clinical interest among the medications examined here, are PPI's like lansoprazole, which are among the most commonly prescribed medications in hospitalized patients despite questionable indications and significant potential side effects. Our data agree with other

studies showing that therapy is frequently initiated for "stress ulcers prophylaxis" in low risk patients as well as for patients who are also prescribed drugs that increase the risk of ulcer [18]. We found that 1 in 5 patients started on a PPI was discharged on one without a labeled indication. Our results, along with others, suggest that initiation of PPI's in hospitalized patients should be more closely evaluated and strongly reevaluated prior to discharge.

A major difficulty in improving evidence-based and safe care via an EMR and CPOE is physician adherence to knowledge imbedded in orders and compliance with CDS. This clearly was a problem in our study. Perhaps greater familiarity with the system and better user interfaces in the future will lead to better accuracy and yield of the indications given.

Though, this study was not designed to measure the impact of linking indication to a medication order on any potential decrease in prescribing errors, these prompts may have benefit in preventing wrong drug and/or patient errors as well as discouraging use in non-evidenced based situations by reminding clinicians of the indications of the medication. Such reminders may cause them to realize that they are in the wrong patient's chart or have selected the wrong medication from a pick list, which is another potentially fruitful area for future research.

5.2 Limitations

Chart review can be limited by poor documentation. For instance, the analysis of discharge medications may have been limited by poor documentation of admission and discharge medications. Further, as evidenced by the 15% disagreement of actual indication by the reviewers, our chart review for indication was imperfect. In addition, this study was conducted at an academic hospital with almost all orders placed by house staff. Generalization to other settings must be done with caution. In particular, the results may be different in institutions with ordering done only by attending physicians.

6. Conclusion

This study illustrates substantial off-label use for certain medications and many challenges for obtaining indication information. In particular, the indication data generated in this pilot study was not highly accurate. The results of this study, as compared to a prior study, suggest that the number of potential indications of a medication may adversely affect the ability to obtain accurate indication data. However, better user interface design may help mitigate this problem. Despite a need for further development, the relatively low cost intervention has the potential to help in collecting valuable information to improve problem list documentation and evidence-based medication use.

Clinical Relevance Statement

The Joint commission requires connection between indications for inpatient medication use and indications approved by a Pharmacy and Therapeutics committee and this type of CDS may help institutions' comply with this regulation. Prompts during CPOE to remind clinicians of a medication's indications may improve evidence based use of medications and can improve problem list documentation. Future versions of this type of CDS may improve the problem list, which in turn should improve the quality of future episodes of care of a patient as well as institutional quality improvement efforts.

Conflict of Interest Statement

None of the authors had any conflicts of interest with this research project.

Protection of Human and Animal Subjects

This project was reviewed, approved, and fully compliant with the IRB at UIC.
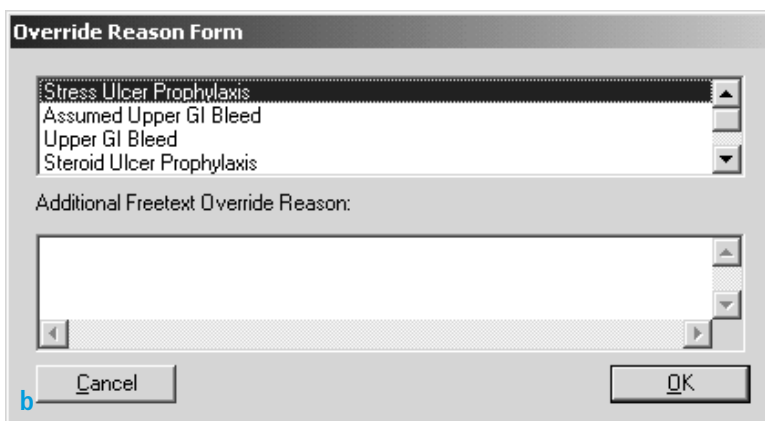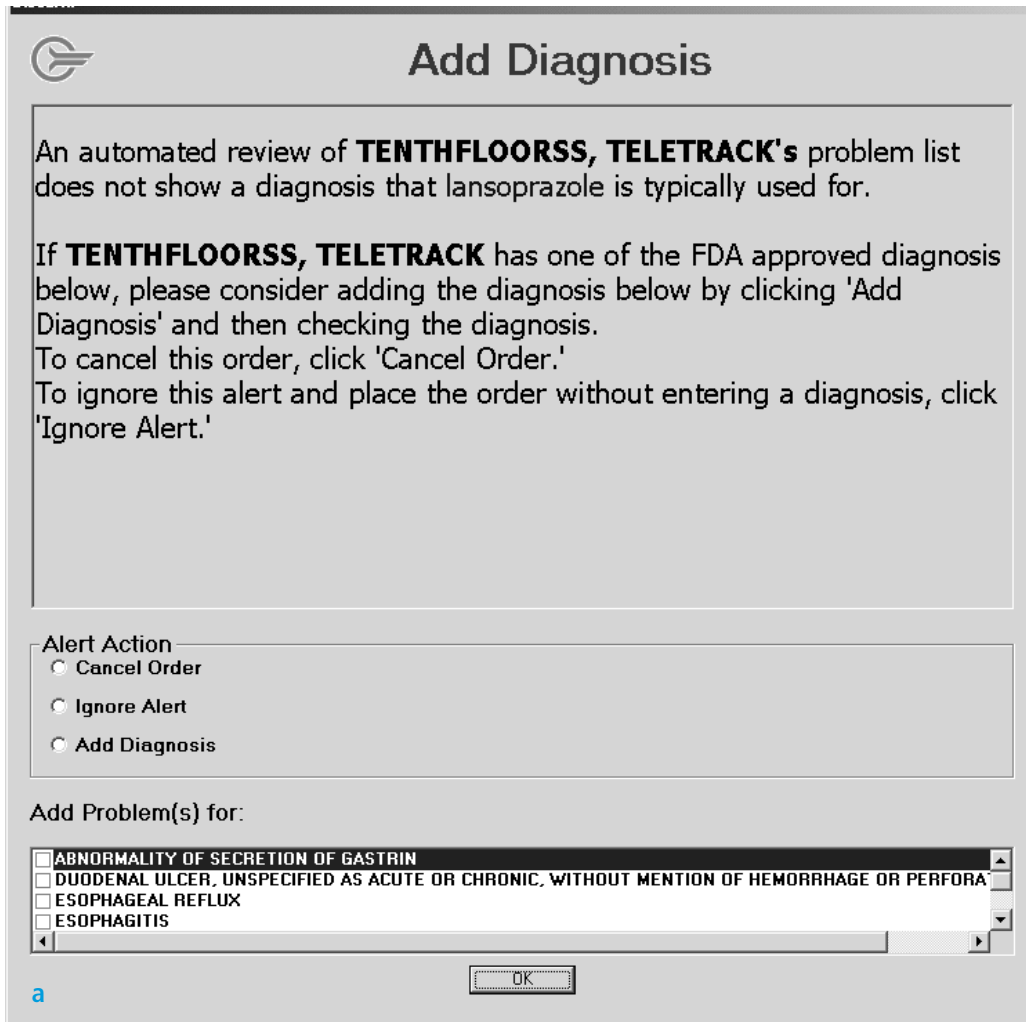
Fig. 1 a) Initial alert when initiating order for lansoprazole b) Subsequent alert when no initial FDA approved diagnosis placed

Table 1 Descriptive characteristics of the observations for the 3 medications

Drug	PPI (Lansoprazole)	IVIG (Flebogamma®)	Factor VIIa (NovoSeven®)
Duration of Trial (days)	60	93	175
Alerts	1404	118	77
Unique Patients	862	59	25
Alerts excluded due to appropriate previously documented diagnosis	332	19	42
Alerts excluded due to a diagnosis placed from a previous alert	69	16	42
Alerts displayed to clinicians	1072	99	25
Admissions with an alert	873	55	25
Study sample size	100	55	25
Yield of indications[1]	*95±2%*	*75±6%*	*96±3%*
Problem list placement yield[1]	*38±5%*	*22±6%*	*64±10%*
Problem list accuracy[1]	*24±7%*	*75±13%*	*38±12%*

[1]Yields and accuracy are presented in terms of mean and standard errors.

Table 2 FDA label and evidence status of actual indications

	PPI Mean ± SE	IVIG Mean ± SE	Factor VIIa Mean ± SE
Indication is FDA Approved[1]	23±4%	9±4%	0%
Indication is off label but evidence based[1]	0%	5±3%	0%

[1]Based on information from the class of drugs.

Table 3 Accuracy of clinician indication compared to actual indication across on and off-labeled uses.

		PPI Mean ± SE	IVIG Mean ± SE	Factor VIIa Mean ± SE
Any labeled indication using the drug class	On label	82±8%	80±20%	NA
	Off label	58±6%	44±8%	29±9%
Any labeled or evidence-based indication using the drug class[1]	Labeled or evidence-based	82±8%	86±14%	NA
	Not labeled or evidence-based	58±6%	41±9%	29±9%
Overall		63±5%	49±8%	29±9%[2]

[1]Note that off-label uses by drug that were on label by class were considered evidence-based in drugdex®

[2]Note that the difference in overall accuracy between Factor VIIa and lansoprazole was statistically significant (P = 0.004), but the difference between IVIG and lansoprazole was not statistically significant (P = 0.12) based on Wald tests of coefficients in a simple logistic regression of accuracy across the drugs.

Table 4 FDA status and evidence base for indications using information by drug and class

Drug	Indications	FDA status/ Evidence based	Percentage of total uses Mean $\pm$ SE
Lansoprazole (Prevacid®)	Gastroesophageal reflux disease (GERD)	FDA approved by class	10$\pm$3%
	Esophagitis	FDA approved by class	2$\pm$1%
	Gastric ulcer	FDA approved by class	1$\pm$1%
	ICU stress ulcer prophylaxis	FDA approved by class	10$\pm$3%
IVIG (Flebogamma®)	ITP: idiopathic thrombocytopenic purpura	FDA approved by class	9.1$\pm$4%
	Guillian-Barré syndrome	Evidence based	5.5$\pm$3%

Table 5 Indication for PPI use in patients discharged on PPI who were not on a PPI prior to admission. Indication was established for lansoprazole use in the inpatient setting and presumed to be the same for the outpatient prescription of a PPI. Note that 77% of these patients were given lansoprazole outpatient and in 23% another PPI was prescribed.

Actual Indication	Number of Patients	FDA Approved Indication for outpatient therapy	Evidence-based indication for outpatient therapy
Bleeding peptic ulcer	1	Yes	Yes
Esophageal reflux	1	Yes	Yes
Nausea	1	No	No
Steroid ulcer prophylaxis	1	No	No
Stress ulcer prophylaxis	17	No	No
Upper GI bleeding	1	No	No

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