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From basic to advanced computerised intravenous to oral switch for paracetamol and antibiotics: an interrupted time series analysis

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ABSTRACT

Objectives Early switch from intravenous to oral therapy of bioequivalent drugs has major advantages but remains challenging. At our hospital, a basic clinical rule was designed to automatically alert the physician to review potential intravenous to oral switch (IVOS). A rather low acceptance rate was observed. In this study, we aimed to develop, validate and investigate the effect of more advanced clinical rules for IVOS, as part of a centralised pharmacist-led medication review service.

Design and setting A quasi-experimental study was performed in a large teaching hospital in Belgium using an interrupted time series design.

Intervention A definite set of 13 criteria for IVOS, focusing on the ability of oral absorption and type of infection, was obtained by literature search and validated by a multidisciplinary expert panel. Based on these criteria, we developed a clinical rule for paracetamol and one for ten bioequivalent antibiotics to identify patients with potentially inappropriate intravenous prescriptions (PIVs). Postintervention, the clinical rule alerts were reviewed by pharmacists, who provided recommendations to switch in case of eligibility.

Primary and secondary outcome measures A regression model was used to assess the impact of the intervention on the number of persistent PIVs between the preintervention and the postintervention period. The total number of recommendations, acceptance rate and financial impact were recorded for the 8-month postintervention period.

Results At baseline, a median number of 11 (range: 7–16) persistent PIVs per day was observed. After the intervention, the number reduced to 3 (range: 1–7) per day. The advanced IVOS clinical rules showed an immediate relative reduction of 79% (incidence rate ratio=0.21, 95% CI 0.13 to 0.32; p<0.01) in the proportion of persistent PIVs. No significant underlying time trends were observed during the study. Postintervention, 1091 recommendations were provided, of which 74.1% were accepted, resulting in a total 1-day cost saving of €4648.35.

Conclusions We showed the efficacy of advanced clinical rules combined with a pharmacist-led medication review for IVOS of bioequivalent drugs.

Strengths and limitations of this study

- ► Previous research has indicated that timely switch from intravenous to oral therapy is an effective and safe measure contributing to rational drug prescribing and leading to cost savings.
- ► An interrupted time series study has been recognised as the strongest quasi-experimental approach to evaluating longitudinal effects of interventions when it is difficult to randomise or identify an appropriate control group.
- ► The advanced rules were tested in the routine clinical practice it was intended for, making the evaluation highly clinically valuable.
- ► This study was performed in a single centre and teaching hospital, limiting the generalisability of the results; however, the rules can easily be transferred to other hospitals working with the same electronic health record, increasing the external validity.
- ► The shorter postimplementation period limited the evaluation of the long-term sustainability of the intervention.

INTRODUCTION

Timely switch from intravenous to oral therapy is an effective and safe measure contributing to an improved rational drug use and leading to cost savings.[1 2] Intravenous to oral switch (IVOS) is favourable for drugs with high bioavailability. In case of comparable plasma exposure (area under the curve (AUC) oral/AUC intravenous 90% CI 0.8 to 1.25), intravenous and oral routes of the same compound at the same dose are considered to be bioequivalent.[1 3] Most of the interventions evaluating IVOS have been restricted to bioequivalent antibiotics.[1 2] However, many more medications are suitable for IVOS, of which paracetamol (88%±15% bioavailability) is the most frequently studied.[4 5]

IVOS has major advantages for the patient (ie, increased mobility and reduced risk of catheter-related complications), the healthcare team (ie, reduced workload and risk of needle stick injuries), the hospital and society (ie, reduced hospital stay and cost), and the

environment (ie, reduced waste).[1 2 6–12] Moreover, an early switch of antimicrobials has been recognised as an easy-to-accomplish antibiotic stewardship intervention, resulting in a more efficient antimicrobial use.[11 13–16]

Yet the overuse of intravenous administrations, when oral formulations may be more appropriate, is highly common.[1] The main obstacle to switch intravenous antibiotics is the misconception that intravenous therapy will reduce the risk of reinfection.[1 7] Prescribers usually tend to choose intravenous antibiotics and paracetamol at the start of the therapy and continue them until discharge, potentially affecting the length of stay.[9 11 17 18] Furthermore, there are conflicting guidelines concerning the criteria and optimal timing for conversion.[17 19 20]

Several strategies to promote IVOS have been evaluated over the years. Proactively contacting the attending physician by a nurse, a pharmacist or an infectious diseases physician with feedback on prescribing has been demonstrated to be useful.[8 9 18 21–23] However, these strategies are time-consuming and costly.[24 25] Also technology-based interventions have been investigated, including computer-generated reminders as part of a computerised physician order entry (CPOE) or clinical decision support system (CDSS).[24–27]

In 2016, a basic clinical rule was designed at University Hospitals Leuven (UZ Leuven) to alert the treating physician to review potential IVOS therapy. The rule screened patients' electronic health records (EHR) based on three criteria: (1) treatment with an intravenous bioequivalent drug in combination with (2) a daily meal order or (3) at least one prescription for another oral drug. When these criteria were met, an automated note was left on the patient's EHR. During an 18-month monitoring period, 22 375 automated notes were sent to alert the treating physician. Although this approach seemed promising, only 52% of the recommendations were accepted by the physician, of which 33% resulted in an actual IVOS and 19% resulted in the discontinuation of the intravenous therapy.[28] This rather low acceptance rate could be attributed to the issue of 'alert fatigue', which is defined as the desensitisation that occurs when physicians are presented with too many (non-relevant) safety alerts.[29]

To mitigate the risk of 'alert fatigue', software-generated recommendations should be interpreted clinically for relevance and communicated to the attending physician by a specified trained person.[30 31] The goal of this study was to develop and validate an advanced IVOS algorithm, as part of a centralised pharmacist-led medication review service, and to evaluate its impact, aiming for a significant reduction in the number of potentially inappropriate intravenous prescriptions (PIVs).

METHODS

Study design and setting

A quasi-experimental study was performed at UZ Leuven, a 1995-bed tertiary care hospital in Belgium. An interrupted time series (ITS) design was used to evaluate the impact of the new algorithm on the number of PIVs.

At UZ Leuven, medication is prescribed electronically using a CPOE on the patient's EHR. Prescribing support is implemented by basic CDSS features embedded in the CPOE to proactively signal clinical problems such as drug–drug interactions, drug–allergy interactions, maximum doses and duplicate therapy. Besides, medication surveillance in inpatients is provided by a centralised clinical pharmacy service, the 'Check of Medication Appropriateness' (CMA). The CMA concerns a hospital-wide and pharmacist-led medication review service, comprising a clinical rule-based screening for potentially inappropriate prescriptions. The CMA is performed by clinical pharmacists, who, if deemed necessary, then provide targeted recommendations to the treating physician.[28 31] Our group recently showed the CMA-based approach to be effective in reducing potentially inappropriate prescriptions.[32 33]

Study population

The advanced algorithm was implemented for all hospitalised patients, with the exclusion of patients admitted to the intensive care unit or palliative care unit. The intervention targeted inpatients treated with intravenous paracetamol or one or more bioequivalent intravenous antibiotics (moxifloxacin, levofloxacin, clindamycin, fluconazole, ornidazole, metronidazole, rifampin, co-trimoxazole and linezolid). Despite showing a bioavailability of 55%±8%, clarithromycin was added to this list, as based on the available intravenous and oral formulations exposure is considered comparable.[4] Pharmacist recommendations were provided to the treating physician, who finally had to decide on treatment adaptation. Patients were therefore not obliged to provide informed consent.

Set-up and implementation of an advanced IVOS algorithm

To identify relevant IVOS criteria, a literature search was performed using the PubMed database. The extracted criteria were then presented to a multidisciplinary expert panel (N=18), representing 2 clinical pharmacists and 16 physicians with different medical specialties. An e-questionnaire, followed by a face-to-face meeting, was conducted to reach consensus among the experts on the identified criteria. A final set of 13 switch criteria, grouped into two categories (ie, ability of oral absorption and type of infection), was obtained.[2 5 11 13–15 25 27 34–40] Of all switch criteria, seven were translated into measurable elements based on structured data available on the EHR. The six criteria regarding the type of infection could not be translated into a computer interpretable condition due to the absence of structurally documented diagnoses on the EHR (table 1). Two clinical rules, one for paracetamol and one for antibiotics, were formulated in the hospital information system by combining these measurable elements in 'if-then' algorithms, with the goal to identify patients with a PIV. Hence, when all seven elements were met, the clinical rules could generate an alert.

During a 3-month validation period (from September 2019 to November 2019), the process was prospectively

Table 1 Definite set of 13 criteria for IVOS grouped into two categories and the associated measurable elements to develop the clinical rules

	Switch criterion	Measurable elements
Category 1: ability of oral absorption (applicable for paracetamol and antibiotics)		
1	Ability to swallow and take oral medications and/or food.	► Absence of NPO instructions. ► Prescription for oral drugs. ► Order for food. ► Absence of mucositis. ► Absence of enteral tube feeding. ► Absence of feeding via TPN. ► Absence of swallowing disorders. ► Absence of acute multifactorial delirium.
2	Absence of nausea and vomiting.	► Absence of nausea registrations. ► Absence of therapy to treat nausea. ► Absence of a nasogastric tube for vomiting-related suction drainage.
3	Absence of severe diarrhoea.	► Absence of diarrhoea registrations. ► Absence of therapy to treat diarrhoea.
4	Absence of ileus or gastrointestinal obstruction.	► Absence of obstruction-related diet.
5	Absence of active gastrointestinal bleeding.	► Absence of therapy to treat upper GI bleeding (high-dose PPI).
6	Absence of a malabsorption syndrome (eg, short bowel syndrome).	► Absence of feeding via TPN.
7	Absence of gastric bypass surgery.	► Absence of bariatric-related diet.
Category 2: type of infection (only applicable for antibiotics)		
8	Exclusion of endovascular infection (eg, endocarditis).	NA*
9	Exclusion of (severe) sepsis and septic shock.	NA*
10	Exclusion of meningitis.	NA*
11	Exclusion of *Staphylococcus aureus* bacteraemia.	NA*
12	Exclusion of CNS infection.	NA*
13	Exclusion of necrotising fasciitis.	NA*

*The criteria regarding the type of infection could not be translated into a computer interpretable condition due to the absence of structurally documented diagnoses on the EHR. These criteria were manually checked by the clinical pharmacist as part of performing the CMA.
CMA, Check of Medication Appropriateness; CNS, central nervous system; EHR, electronic health record; GI, gastrointestinal; IVOS, intravenous to oral switch; NA, not applicable; NPO, nil per os; PPI, proton pump inhibitor; TPN, total parenteral nutrition.

validated by evaluating all alerts generated by running the rules behind-the-scene on inpatients. The results of the clinical rules were compared with a manual review of the EHR, performed by two researchers (CQ, MCo). The rule effectiveness was measured as the proportion of correct alerts on the total number of generated alerts. It describes the ability of the algorithm to correctly screen and identify the predefined measurable elements (table 1) on the patient's EHR. Overall, 99% of the alerts were classified as correctly generated by the clinical rule, with a rule effectiveness for IVOS of paracetamol and antibiotics of 99% and 98%, respectively.

The validated advanced IVOS clinical rules were implemented in the daily CMA service in December 2019. The CMA is performed each afternoon from Monday until Saturday in a 0.6 full-time equivalent service. The rule-based screening ran continuously on real-time and dynamic patient data, which makes it able to identify rapid changes in the patient's condition. The clinical rule alerts were listed on the CMA worklist. Clinical pharmacists reviewed this worklist on a daily basis. The switch criteria regarding the type of infection were manually checked during this review process. In case the patient was eligible for IVOS, a recommendation to switch was provided by the clinical pharmacist by adding a note to the patient's EHR for the treating physician.

Clinical pharmacists were trained to perform the medication review. Furthermore, a user-friendly validated flow chart was developed, on which the hospital pharmacist could rely while performing the medication review, in order to achieve uniformity (online supplemental file 1). Inter-rater reliability between pharmacists has already been proven during the initial validation of the CMA service.[28]

Data collection

A quasi-experimental ITS study was performed to estimate the effect of the advanced IVOS rules, integrated in the CMA, on the number of persistent PIVs. This ITS design is characterised by a series of measurements over time interrupted by an intervention, that is, the advanced IVOS rules. The daily number of persistent PIVs was recorded for a sample of randomly chosen days in the preintervention period (from December 2015 to March 2019) and the postintervention period (from December 2019 to July 2020). A main analysis for all PIVs as well as an analysis for paracetamol and an analysis for antibiotics were conducted.

For the preintervention period, data collection was performed retrospectively by two researchers (CQ, MCo). An initial PIV (PIV at T_0) was identified by running the clinical rules in the EHR on retrospective patient data, followed by a manual review. A persistent PIV was then defined if the same PIV persisted present after T_0+48 hours. For the postintervention period, an initial PIV was identified prospectively in the CMA performed by a team of trained clinical pharmacists, that is, by running the rules in real time on prospective patient data. For each identified PIV at T_0 in the CMA, a recommendation was formulated by the clinical pharmacist for which the acceptance within 48 hours was registered. A persistent PIV was identified in case a PIV was still present after T_0+48 hours, that is, due to non-acceptance of the recommendation. For both the preintervention and the postintervention period, the number of initially observed PIVs, the number of patients, patient demographics (age, gender) and medical discipline were also documented.

For the postintervention period, a descriptive analysis was performed during the first 8 months after implementation (from December 2019 to July 2020). The number of generated alerts, the number of pharmacists' recommendations and the proportion of acceptance by physicians were documented. Patient-related data were extracted from the EHR and included the patient's age and gender, drug name, hospital ward and medical discipline. The acceptance rate was assessed by reviewing the EHR. Acceptance was defined as changing the route of administration from intravenous to oral, initiating the oral drug in addition to the intravenous therapy, or discontinuing the intravenous therapy within 48 hours after the pharmacist's recommendation. In case of discharge, death or transfer to an intensive care unit within 48 hours or an altered therapy or patient situation (eg, change in clinical parameters) that resulted in the PIV no longer being present within 48 hours, acceptance was classified as 'unassessable'. These 'unassessable' recommendations were excluded in the evaluation of the acceptance rate and the number of residual PIVs. Reasons for not accepting the pharmacists' recommendations and the clinical consequences of non-adherence were not systematically investigated. For all accepted IVOS recommendations a total 1-day cost saving was calculated assuming that at least 1 day of oral therapy was given instead of intravenous therapy. Therefore, the difference in cost between intravenous and oral therapy per day was calculated for each specific drug treatment. This was determined for the most common doses, taking into account drug costs and intravenous-related administration costs (ie, cost of infusion line and infusion bag). Costs were expressed in euros using 2019 Belgian public market prices.

Statistical analysis

To compare the distribution of included patients between the preintervention and the postintervention period, a Wilcoxon rank-sum test was used for continuous data and χ^2 test for categorical data.

By modelling the ITS data using a segmented regression analysis, both the time trend of each period and the immediate intervention's effect were investigated.[40] In the segmented regression model, the estimated effects were expressed as incidence rate ratio (IRR). The incidence rate (IR) was defined as the number of persistent PIVs divided by the number of initially identified PIVs at T_0. The IRR quantified the relative increase or decrease of the IR as a result of intervention or time.

The model is specified as[41]:

$Y_t = \beta_0 + \beta_1 \text{time}_t + \beta_2 \text{intervention}_t + \beta_3 \text{time after intervention}_t + \varepsilon_t$

- Y_t is the value of the dependent variable (IR) in month t.
- Time is a continuous variable indicating time in months at period t, whereby time is centred at the intervention.
- Intervention is an indicator for time t occurring before or after implementation.
- Time after intervention is a continuous variable counting the number of months after the intervention at time t.
- β_0 estimates the preintervention IR of persistent PIVs at the beginning of the time series.
- β_1 estimates the preintervention trend.
- β_2 estimates the immediate change in the level of the IR after implementation of the intervention.
- β_3 estimates the change in the trend after implementation.
- ε_t is an estimate of the random error.

To calculate a power-based sample size, a mean number of 16 recommendations per day for IVOS was considered. To detect an expected decrease of 50% in the primary outcome with a power of 95%, 12 data points (using days as data points) in each period were required. To ensure that a stable estimate of the baseline underlying secular trend would be obtained, 12 days spread over 4 months from December to March were analysed for each year in the preintervention period (from December 2015 to March 2019), totalling up to 48 data points. For the postintervention period, the same 12 days, supplemented by 12 extra days (to estimate a more reliable effect of time), were analysed from December 2019 to July 2020, totalling up to 24 data points.

The segmented regression analysis was performed using SAS software (V.9.4). Estimated effects with 95% CIs were calculated. P<0.05 was considered statistically significant.

For the postintervention period, descriptive analyses were performed. The positive predictive value (PPV), that is, the probability of alerts leading to recommendations, was measured as the ratio of the total number of pharmacists' recommendations to the total number of alerts generated.

Patient and public involvement

Pharmacists' recommendations were provided directly to the treating physician, who finally had to decide on treatment adaptation. Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

ITS analysis

For the 48 data points in the preintervention period, 733 initial PIVs were observed in 698 inpatients. Postintervention, 460 initial PIVs were observed in 414 patients during 24 days. There was no significant difference in the distribution between both periods according to patient demographics (age, gender). In the postintervention period, significantly fewer patients with an initial PIV were admitted to the gastroenterology ward (p<0.01) (table 2).

Preintervention, the median proportion of all persistent PIVs was 65.9% (range: 41.7%–100%), with a median number of 11 (range: 7–16) persistent PIVs per day. After implementing the advanced rules, the median proportion and median number decreased to 17.3% (range: 3.2%–44.4%) and 3 (range: 1–7), respectively (figure 1A). The results of the regression model indicated that, at the start of the preintervention period (December 2015), the IR was 67.9% (β_0). The IRR for level change due to the intervention was 0.21 (β_2; CI 0.13 to 0.32), meaning that postintervention the IR was 21% of the preintervention IR, indicating a significant immediate relative reduction of 79% (p<0.01) in persistent PIVs. Neither a significant underlying time trend was observed during both the preintervention (β_1) and the postintervention period, nor a significant difference when comparing preintervention and postintervention trends (β_3) (figure 1B, table 3).

The intervention showed an immediate relative reduction of 82% (p<0.01; 95% CI 0.10 to 0.32) and 73% (p<0.01; 95% CI 0.12 to 0.61) in the proportion of persistent PIVs for paracetamol and for bioequivalent antibiotics, respectively (table 3).

Descriptive analyses in the postintervention period

During an 8-month period, 2265 clinical rule alerts were generated and reviewed. The clinical pharmacists provided 1091 recommendations for 913 individual patients during 961 hospital admissions, resulting in an overall PPV of 48.2%. A higher PPV was observed for the clinical rule for paracetamol (ie, 53.3%) than for the rule targeting antibiotics (ie, 37.4%). Also, more recommendations were provided for paracetamol (n=817) than for antibiotics (n=274). The mean age of patients for whom a recommendation was given was 64.9 years (SD ±19.4), and 54.7% of patients were men. Recommendations were most frequently formulated for patients admitted to an internal medicine ward (11.2%), hepatology ward (9.7%), pulmonary ward (8.8%) and geriatric ward (8.4%). Acceptance could be assessed for 798 recommendations, of which 74.1% (n=591) were accepted by the treating physician. A slightly higher acceptance rate was obtained for the recommendations for antibiotics (76.9%) compared with those for paracetamol (73.1%). The details on the number of pharmacists' recommendations and the acceptance rate for each individual drug are specified in table 4. Taking into account the recommendations for combination therapy, 591 accepted recommendations resulted in 609 IVOS interventions. All these IVOS interventions resulted in a total 1-day cost saving of €4648.35, based on the difference in cost between intravenous and oral therapy (online supplemental file 2).

Table 2 Characteristics of the identified initial PIVs in the preintervention and postintervention period of the ITS analysis

Characteristics	Preintervention period	Postintervention period	P value
Data points (days), n	48	24	
Initial PIVs at T_0, n	733	460	
Patients, n	698	414	
Demographics			
Age (years), mean±SD	62.8±20.5	65.0±19.5	0.13
Female, n (%)	299 (42.8)	195 (47.1)	0.19
Medical discipline, n (%)	733 (100)	418* (100)	**<0.01**
Geriatrics	69 (9.4)	33 (7.9)	0.44
General internal medicine	67 (9.1)	45 (10.8)	0.43
Gastroenterology	65 (8.9)	13 (3.1)	**<0.01**
Hepatology	62 (8.5)	45 (10.8)	0.23
Pulmonology	62 (8.5)	37 (8.9)	0.90
Haematology	45 (6.1)	23 (5.5)	0.76
Nephrology	44 (6.0)	16 (3.8)	0.14
Gastrointestinal oncology	36 (4.9)	20 (4.8)	1
Gynaecological oncology	36 (4.9)	12 (2.9)	0.13
General medical oncology	32 (4.4)	25 (6.0)	0.28
Other	215 (29.3)	149 (35.6)	

P value <0.05 was considered statistically significant.
*For 42 initial PIVs in the postintervention period the medical discipline could not be recorded.
ITS, interrupted time series; PIV, potentially inappropriate intravenous prescription.

DISCUSSION

Our study showed that the advanced IVOS clinical rules improved switch therapy impressively, as the number of persistent PIVs was reduced by 79%. This effect was significant and sustained. The optimisation of the clinical rules was associated with an almost perfect rule effectiveness, a high PPV and a high acceptance rate. These results hence promote the use of advanced rules combined with a pharmacist-led medication review service to improve IVOS.

Many strategies have already been described to overcome barriers for early IVOS. For example, some hospitals are embedding CDSS to generate IVOS alerts at the moment of prescribing.[24 26] However, an ITS analysis, performed by Hulgan *et al*[26] in which the effect of CDSS on IVOS of quinolones was investigated, showed only a limited increase of 5.6% in oral orders. In the study of Fischer *et al*[24] only 35.6% of all orders for which an alert was generated resulted in either a conversion or therapy

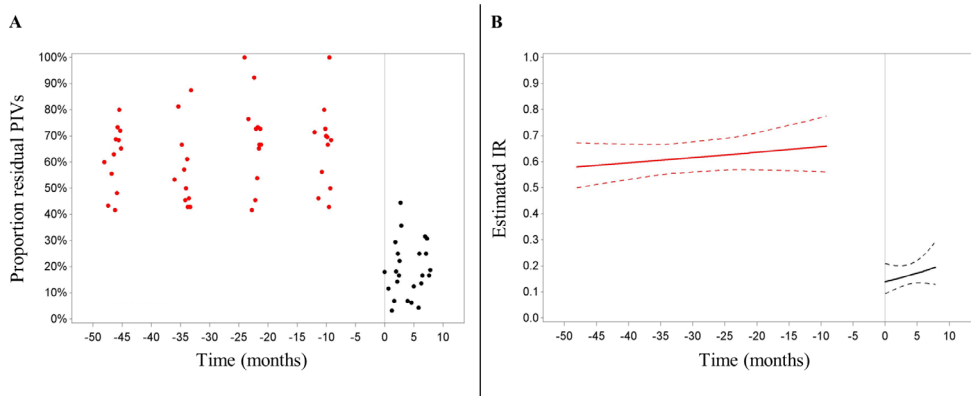

Figure 1 (A) Observed proportions of all persistent PIVs per day for the 48 days in the preintervention period (red) (ie, the same 12 days spread over 4 months from December to March for 4 years) and for the 24 days spread over 8 months from December to July in the postintervention period (black). (B) Estimated IR (with 95% CI) of all persistent PIVs over time and by period showing the difference between the preintervention period (red) and the postintervention period (black). Time is centred at the intervention, taking a value of 0 month at intervention, positive values in the postintervention period and negative values in the preintervention period. IR, incidence rate; PIV, potentially inappropriate intravenous prescription.

Table 3 Parameter estimates (with 95% CI), SE and p values of the ITS analysis

		Estimate (95% CI)	SE	P value
All persistent PIVs	Intercept (β_0)	0.68 (0.55 to 0.84)	0.11	<0.01
	Preintervention trend (β_1)	1.00 (1.00 to 1.01)	<0.01	0.32
	Change in level after the intervention (β_2)	0.21 (0.13 to 0.32)	0.23	**<0.01**
	Postintervention trend	1.04 (0.96 to 1.14)		0.34
	Change in trend after the intervention (β_3)	1.04 (0.95 to 1.13)	0.04	0.38
Persistent PIVs for paracetamol	Intercept (β_0)	0.66 (0.52 to 0.84)	0.12	<0.01
	Preintervention trend (β_1)	1.00 (1.00 to 1.01)	<0.01	0.38
	Change in level after the intervention (β_2)	0.18 (0.10 to 0.32)	0.28	**<0.01**
	Postintervention trend	1.08 (0.97 to 1.19)		0.15
	Change in trend after the intervention (β_3)	1.07 (0.97 to 1.19)	0.05	0.17
Persistent PIVs for antibiotics	Intercept (β_0)	0.74 (0.47 to 1.17)	0.23	0.20
	Preintervention trend (β_1)	1.00 (0.99 to 1.02)	<0.01	0.63
	Change in level after the intervention (β_2)	0.27 (0.12 to 0.61)	0.42	**<0.01**
	Postintervention trend	0.96 (0.81 to 1.13)		0.62
	Change in trend after the intervention (β_3)	0.95 (0.80 to 1.13)	0.09	0.59

P value <0.05 was considered statistically significant.
ITS, interrupted time series; PIV, potentially inappropriate intravenous prescription.

discontinuation. Berrevoets *et al*[25] combined automated reminders relying on a stand-alone software tool with a weekly educational session. An ITS analysis showed only a moderate reduction of 19% in prolonged intravenous prescriptions. These results indicate a limited clinical relevance of alerts, with the risk of causing prescribers' alert fatigue.[29] To mitigate the risk of alert fatigue, Akhloufi *et al*[34] developed an IVOS algorithm that sent alerts directly

Table 4 Number of recommendations and acceptance rate for the individual drugs

Drug	Recommendations (n)	Acceptance rate (%)
Paracetamol	817	73.1
Clindamycin	64	84.3
Levofloxacin	61	80.4
Fluconazole	35	54.2
Ornidazole	32	73.7
Clarithromycin	21	70.0
Metronidazole	17	71.4
Co-trimoxazole	8	20.0
Moxifloxacin	6	100.0
Linezolid	4	100.0
Rifampin	–	–
Combination therapy	26	94.7
Levofloxacin+ornidazole		
Levofloxacin+clindamycin		
Levofloxacin+fluconazole		
Levofloxacin+metronidazole		
Moxifloxacin+metronidazole		
Moxifloxacin+ornidazole		
Clarithromycin+ornidazole		
Total	1091	74.1

to the infectious disease specialist of the antibiotic stewardship team, resulting in advice to change the antibiotic policy in 10.1% of the screened prescriptions.[27 34] In our intervention, the risk of alert fatigue among physicians was reduced by generating alerts exclusively to trained pharmacists who reviewed these for clinical relevance. Physicians hence were only warned of an intravenous prescription considered as definitely inappropriate by the pharmacist, leading to a high acceptance rate. Alert fatigue among pharmacists was countered by increasing the specificity of the clinical rules by incorporating as much as possible patient-related structured data as measurable elements. This resulted in a PPV of 48.2%. Further optimisation of the PPV depends on further structural digitalisation of patients' data on the EHR. For example, some reasons for inability of oral intake were only mentioned by the physician or nurse in unstructured free text fields. Moreover, the type of infection could not be screened for due to the lack of structurally documented diagnoses, also resulting in a lower PPV of the rule for antibiotics compared with that for paracetamol. In our opinion, the lack of specific structural data emphasises the importance of the role of a specified trained person, for example, a pharmacist, to review the alerts before these are sent to physicians.[30 31] In the future, it seems valuable to further focus on the digital structuring of patient data.

The observational study showed differences in the number of recommendations between the individual antibiotics. This could be a result of the local prescribing behaviour and institutional guidelines. For example, 65% of the recommendations were provided for patients treated with clindamycin, levofloxacin, ornidazole and clarithromycin, which are typically preferred drugs for initial empiric therapy at our hospital. This illustrates the misconception among prescribers that intravenous empiric therapy is more potent.[35 42 43] By contrast, the limited number of alerts generated for moxifloxacin, linezolid and rifampin can possibly be attributed to their restricted use.

Non-acceptance of recommendations for paracetamol could possibly be explained by prescribers' preference for intravenous paracetamol due to observations of a faster reduction of fever when administered intravenously. This was already demonstrated by studies comparing the efficacy and safety of intravenous and oral paracetamol. A single dose of intravenous paracetamol was found to be as safe and effective in reducing fever as oral paracetamol. Yet an earlier onset of action was achieved with the intravenous formulation.[44 45] Hence, as intravenous administration of paracetamol is only justified when rapid reduction of temperature is desirable, IVOS should be encouraged.

Previous studies already showed that verbally communicated pharmaceutical recommendations are more likely to be accepted by physicians.[46] As a result, contacting the physician by phone could further increase the acceptance rate and could give insights into physicians' concerns about patient outcome when prescribing oral therapy. For example, Berrevoets *et al*[25] combined a computerised intervention with an educational programme. Furthermore, Vogtländer *et al*[47] concluded that unawareness of the principles of switch therapy was the most important barrier to IVOS therapy. Hence, combining our advanced rules with a poster campaign, hospital-wide education of the validated switch criteria or providing switch guidelines might improve our intervention even more.[23]

Our study clearly indicates that IVOS is associated with lower costs. Since no data were collected on the duration of therapy, only a 1-day cost saving was calculated for the most common doses, taking into account the cost of drugs, infusion bags and infusion lines. This is just a minimal cost saving, where in reality the benefit is estimated to be greater due to a longer duration of oral instead of intravenous therapy, use of higher doses, savings from avoiding infusion-related complications and line reinstallations, and savings from reducing the wage cost associated with compounding and administration of intravenous therapy and potentially reducing length of stay.

The present study has several strengths. First, the advanced rules were tested in the routine clinical practice it was intended for, making the evaluation highly clinically valuable and the results very useful. Next, considering possible modifications, the advanced IVOS algorithm, integrated in the EHR, can easily be transferred to other Belgian hospitals working with the same system and also replicated in other hospitals based on the details of the validated criteria and measurable elements (table 1). In Belgium, 30 other hospitals are already using the same hospital information system, covering almost 2 000 000 patients in 2019, and international dissemination is also expected. Third, an ITS design has been recognised as the strongest quasi-experimental approach to evaluating longitudinal effects of interventions when it is difficult to randomise or identify an appropriate control group.[41] The regression analysis accounts for the baseline IR and trend and visually displays well the secular trends in the outcome measure.[48]

Also a number of limitations should be mentioned. First, as this study was performed in a single centre and teaching hospital, the generalisability of the results to other hospitals is unclear. Second, false negative alerts (or missed alerts) were not studied due to practical considerations. However, the primary goal of our study was to obtain a sufficiently high proportion of alerts resulting in a recommendation, reported as the PPV. Developing clinical rules with a high PPV and a subsequently lower risk of pharmacists' alert fatigue was considered more important than obtaining a very sensitive rule. Third, due to the lack of a control group or drug, potential confounding from simultaneous events occurring around the time of the intervention cannot be excluded. Next, the shorter postintervention period limited the evaluation of the sustainability of this intervention. However, our research group recently showed in ITS analyses the long-term sustainability of the CMA approach for other clinical rules focusing on analgesic and antimicrobial prescribing.[32 33]

Furthermore, in this postintervention period, the analysis for the same 12 data points was supplemented with 12 additional data points in 2020 to extend the period. However, these 12 additional data points from April to July were not explored in the preintervention period. In this way bias due to seasonality cannot be completely excluded when estimating the postintervention trend. However, the main concerns of our ITS analysis were (1) estimating the difference in level between both periods and (2) estimating the difference in time trend between both periods, corrected for any time evolution in the preintervention period. Both effects can be estimated in an unbiased fashion based on the selected data points.

In the future, it might be advisable to assess the long-term sustainability of the intervention in a follow-up study with a longer postintervention period. Furthermore, the outcome of PIVs did not directly measure clinical benefits to both the patient and the healthcare system. Investigating the impact on adverse drug events and length of stay and a more extended and thorough cost-effectiveness analysis should be part of future investigations. Regarding the latter, a pragmatic approach to perform cost-effectiveness analyses of centralised clinical pharmacy services was already proposed and applied to three specific clinical rules of the CMA.[49] Next, in our study, the most common bioequivalent drugs at our hospital were covered. By integrating a wider range of bioequivalent drugs, more inappropriate intravenous prescriptions can be avoided.[4] Moreover, when considering proper dose adjustments, a wider range of intravenous drugs, apart from bioequivalence, might be targeted for switch therapy.

In summary, our ITS study showed that performing a centralised medication review, in patients triggered by specific advanced clinical rules, by trained clinical pharmacists leads to an immediate significant reduction of 79% in persistent PIVs. This approach, mainly based on the availability of a full and integrated EHR, a robust screening algorithm capable of identifying triggers in the EHR in a continuous way and conducting targeted medication reviews, helps to optimise early switch from intravenous to oral therapy of bioequivalent drugs in inpatients.

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Ethics approval This study involves human participants and was approved by the institutional and/or national research committee (Ethics Committee Research UZ Leuven, Belgium; S61615). Pharmacist recommendations were provided to the treating physician, who finally had to decide on treatment adaptation. Patients were therefore not obliged to provide informed consent.

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