

BMJ Open Quality Transition from a dedicated to a non-dedicated, ward-based pharmacist antimicrobial stewardship programme model in a non-academic hospital and its impact on length of stay of patients admitted with pneumonia: a prospective observational study

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ABSTRACT

Pharmacists play an integral role in antimicrobial stewardship (AS). Some AS programmes employ dedicated pharmacists, sometimes with infectious diseases (ID) training, while others employ ward-based pharmacists. The role and impact of both are under investigation. This study compares the length of stay (LOS) of patients admitted to hospital with community-acquired pneumonia (CAP) after the implementation of an AS programme initially led by a dedicated ID-trained pharmacist, and then transitioned to a ward-based pharmacist. Starting 1 April 2013, all adult patients admitted with CAP were prospectively reviewed by the AS programme. The control period (phase 0) lasted 3 months. Thereafter, AS was implemented in each of four medicine wards at 2-month intervals in a staggered fashion. During this period (phase 1), an ID-trained pharmacist and physician performed daily prospective audit and feedback. After 24 months, ward-based pharmacists assumed this AS role (phase 2). Over the 36-month study period, 1125 patients with CAP were entered into the AS database, with 518 and 247 patients receiving an AS audit and feedback in phases 1 and 2, respectively. The acceptance rate for AS recommendations was similar for phases 1 and 2, each exceeding 82%. After accounting for secular trends, the overall reduction in LOS was 19.4% (95% CI 1.4% to 40.5%). There was no difference in LOS between phases 1 and 2. This study demonstrated that an AS audit and feedback intervention reduced the median LOS in patients with CAP by approximately 0.5 days regardless of pharmacist model. However, fewer patients were exposed to the AS intervention in phase 2, suggesting dedicated AS pharmacists may be necessary to realise the full benefits of AS.

PROBLEM

Since April 2013, our 339-bed, acute care, community-based hospital located in Barrie, Ontario, Canada, has had an antimicrobial stewardship (AS) programme led by

a dedicated 0.8 full-time equivalent (FTE) infectious diseases (ID)-trained pharmacist and a 0.2 FTE ID-trained clinician researcher. We modelled our approach after the 'Start Smart-Then Focus' AS programme employed across acute care trusts in the National Health Service.¹ In addition, we embedded two research projects a priori into the AS programme to ensure that we could evaluate the effectiveness of our approach in reducing both the length of stay (LOS) in patients admitted to hospital with community-acquired pneumonia (CAP) and the incidence rate of *Clostridium difficile* infection.^{2,3} Like other AS programmes, ours has continued to evolve. The biggest change has been the transition from one where both the ID-trained pharmacist and physician were responsible for every AS audit on each medical ward, to one where the AS audits were done by the ward-based pharmacists as part of their daily routine. This transition was done out of necessity to accommodate the expansion of our AS programme to the surgical wards in the hospital. Our concern was that the gains our AS programme had achieved in reducing antibiotic utilisation without negatively impacting on LOS, mortality rates or 30-day readmission rates might be lost in the transition. This study examines the impact of this transition on CAP LOS.

BACKGROUND

Accreditation Canada, Canada's hospital accreditation organisation, declared that AS should be a required organisational practice for acute care hospitals in 2013.⁴ As a result,

hospitals must implement an AS programme to promote optimal antimicrobial use to be eligible to receive Accreditation Canada's highest award.⁵ This singular change in hospital accreditation policy was likely the tipping point in convincing previously reticent hospital administrators to fund AS programmes.⁶ While Accreditation Canada does not endorse any specific AS model, the Society of Infectious Disease Pharmacists and the American Society of Health-System Pharmacists have recently suggested that all AS pharmacists should ideally be ID-trained, or at the very least have AS-specific training,⁷ despite the absence of evidence to support these recommendations.^{8–10} More importantly, the combination of *dedicated time* to target *uncomplicated* issues, such as the duration of treatment for common clinical syndromes like pneumonia, is more likely to be relevant to pharmacist-led AS programme success than any formalised training requirements or attempted AS interventions in highly complex patients such as those admitted to intensive care units.^{11–15}

MEASUREMENT

For the entire 3-year study period, both the ID-trained pharmacist and physician collected the following patient data on admission: age group (deciles), sex (male/female), Charlson Comorbidity Score¹⁴ (score based on the presence of 12 possible comorbidities, and predictive of all-cause mortality 1 year after hospital discharge), CURB-65 score¹⁵ (score based on the presence of Confusion, elevated Urea, elevated Respiratory rate, low Blood pressure and age ≥ 65 years, and predictive of in-hospital pneumonia-related mortality), presence of acute radiological changes (yes/no as interpreted by radiologist), presence of Halm's criteria¹⁶ (yes/no for each of fever, hypoxia, tachypnoea, hypotension and confusion), medical ward of admission, and date, day and time of admission.

Each patient record was reviewed daily until hospital discharge, censoring (at 14 days after admission) or other competing outcome (death, admission to an intensive care unit or transfer to another acute care hospital). The following patient data were collected after admission: AS audit and feedback (yes/no), date of AS intervention, AS recommendation acceptance by attending physician (yes/no), intravenous days of antimicrobial therapy (DOT; every day that an intravenous antibiotic was administered to the patient regardless of dose or frequency was counted as 1 DOT; if two different antibiotics were delivered intravenously on the same day, then each antibiotic contributed 1 DOT to the total), time to clinical stability (days from admission when every abnormal Halm's criteria had normalised), time to oral intake (days from admission when patient consumed $\geq 50\%$ recommended caloric intake), presence of complications (lung abscess, empyema or pleural effusion needing drainage), and date and time of outcome.

The primary outcome was LOS for patients discharged alive from hospital (=date and time of discharge – date

and time of admission). LOS was modelled as a time to event outcome. Administrative censoring at 14 days after admission was decided a priori. Competing events were included in the model. Competing events were defined as events that preclude the occurrence of the primary outcome and included admission to an intensive care unit after being admitted to a ward, death or transfer to another acute care facility. Competing risks semiparametric survival analysis was used to estimate the average effect of the AS intervention on LOS.

Time to AS intervention (=date of AS intervention – date of admission) was modelled as a time-varying covariate by splitting the observation period of each patient record with an AS intervention into two segments: one before and one after the AS intervention. For example, if a patient was admitted to hospital on day 0, and had an AS intervention on day 4, and was discharged alive on day 10, then this record would be divided into two segments: segment 1 extends from day 0 to day 4 with the outcome recorded as censored, and segment 2 extends from day 4 to day 10 with the outcome recorded as discharged alive. This splitting ensures that only those patient days at risk after an AS intervention are used to calculate the AS intervention hazard rate for live discharge, thus reducing the chance of a false-negative result. Time to clinical stability and time to oral intake were also modelled as time-varying covariates in the final model.

Secular trends for LOS for each medical ward were included in the final model by using an interaction term between each ward and time (number of months) since April 2013. Given the observational nature of the study and the risk of selection bias as a result of confounding by indication, propensity scores (PS) to estimate the conditional probability of exposure to the AS intervention for each patient were calculated using a logistic regression model that included the following variables: CURB-65 score, Charlson Comorbidity Index, age group, sex, Halm's criteria, radiological changes, empirical use of intravenous antibiotics, day of week of admission, and an interaction term between ward of admission and phase of study (1, 2 or 3). The PS was then used to calculate the inverse probability of the treatment weights for the treated ($1/PS$) and untreated ($1/(1-PS)$) patients.¹⁷ Variables included in the final model were the same variables included in the logit PS model, except the interaction term between ward of admission and phase of study was replaced by the secular trend variables, to ensure a 'doubly robust' analysis to guard against model misspecification.¹⁸ In addition, interaction terms between AS exposure and total days of intravenous therapy and AS exposure and AS recommendation acceptance were tested for inclusion in the final model using the Akaike's information criterion (AIC) and Bayesian information criterion (BIC).

The average AS intervention effect is reported as a subhazard ratio (SHR) that is interpreted as the ratio of the probabilities of hospital discharge in patients exposed to AS compared with those not exposed and in whom a competing event has not yet occurred.¹⁹

An SHR >1 means that LOS is reduced in AS-exposed patients compared with unexposed patients as a result of an increased *hazard rate* of hospital discharge in the AS-exposed group, whereas an SHR <1 means that AS-exposed patients have a longer LOS than unexposed patients, and an SHR=1 means there was no difference in LOS between the two groups.¹⁹ Comparisons between continuous and categorical summary statistics by AS exposure status were done using a t-test or Pearson's χ^2 test, respectively.

The secondary outcome was total DOT per patient. DOT was right-skewed, with a range from 1 to 58. DOT was log-transformed and modelled using simple linear regression. The final model included all the following variables chosen a priori: Charlson Comorbidity Score, CURB-65 score, time to clinical stability, CAP criteria, ward of admission, age, sex, AS intervention and presence of complicated CAP.

DESIGN

The methodology for this study has been published elsewhere.² Briefly, all adult patients (≥ 18 years old) admitted to hospital with a diagnosis of CAP by their attending physicians were prospectively identified and followed by the AS programme. CAP was defined as a lower respiratory tract infection in a patient who had not had any previous hospitalisation of ≥ 48 consecutive hours in the prior 3-month period.²⁰

Audit and feedback were the primary AS intervention used throughout the study. Basically, the AS team identified patients with CAP, collected data prospectively, and audited patients Monday to Friday starting at ≥ 48 hours after admission if patients met the following criteria: (1) were admitted to a ward, and (2) were receiving any intravenous antibiotics ≥ 48 hours, or were receiving any oral fluoroquinolone (moxifloxacin or levofloxacin), oral quinolone (ciprofloxacin) or oral cephalosporin (cefprozil or cefuroxime) for ≥ 48 hours, or were receiving ≥ 5 days of any antibiotic. The AS team then made recommendations to the attending physician; these were documented in the electronic medical record, along with documenting the recommendations in the physician order section of the patient's paper chart as suggestions that required attending physician agreement and sign-off prior to implementation, and direct verbal communication with the attending physician whenever possible or deemed necessary. Agreement was considered to have occurred if the attending physician signed off on the AS recommendations within 24 hours. The AS recommendations could be any one or more of the following: (1) no change to current therapy, (2) intravenous to oral conversion, (3) discontinue antibiotic therapy, (4) change in duration or dose, and (5) de-escalation or escalation of antibiotic therapy.¹ These recommendations were not mutually exclusive, and it was common for the AS team to make more than one recommendation for the same patient.

Ward	Phase														
	1			2										3	
	Month														
	1	2	3	4	5	6	7	8	9	10	11	12	13-24	25-36	
3GA	x	x	x	AS	AS										
3GC	x	x	x	x	x	AS	AS								
4GC	x	x	x	x	x	x	x	AS	AS	AS	AS	AS	AS	AS	
3SA	x	x	x	x	x	x	x	x	x	AS	AS	AS	AS	AS	

AS= intervention X= no intervention (control intervals)

Figure 1 Stepped-wedge implementation of the antimicrobial stewardship programme over a 36-month study period.

STRATEGY

From 1 April to 30 June 2013, all patients with CAP admitted to the hospital served as strict controls (phase 1). Over the next 8 months, each of the four medical wards was exposed to AS using a staggered implementation at 2-month intervals. This staggered implementation was done for both pragmatic human resource limitations, but also to provide contemporaneous controls for the AS-exposed patients during this phase. By 1 January 2014, all four wards were exposed to AS, and this phase continued until 31 March 2015 (phase 1). An ID-trained pharmacist and ID-trained physician were responsible for every AS audit and feedback in phase 1. From 1 April 2015 to 31 March 2016 (phase 2), ward-based pharmacists became responsible for AS audit and feedback to permit the dedicated AS team members to expand their activities onto the surgical wards (figure 1).

In advance of phase 2, the ward-based pharmacists were provided with the Infectious Disease Society of America CAP treatment guidelines and instructed on their rationale and interpretation by the AS team. In addition, a series of web-based teaching vignettes were provided on a monthly basis for the pharmacists to complete. The pharmacists were required to complete the questions associated with the vignettes, and then were provided with feedback from the AS team. In total, there were six vignettes. Beyond this, these ward-based pharmacists had no extra training or dedicated time to support their AS activities, but they had the option of reviewing their AS audits and recommendations on a daily basis with the dedicated ID-trained pharmacist and ID-trained physician.

The Royal Victoria Regional Health Centre Research Ethics Board waived the need for informed consent given the AS programme had already been approved for implementation by the hospital, there was minimal risk of harm to the patient, and every AS recommendation would necessarily require the attending physician to receive informed consent from the patient prior to implementation as per the usual process of care.

Stata/MP V.14.1 was used for all statistical analyses.

RESULTS

Over the 3-year study period, 1698 patients were screened for eligibility and 1125 patients with CAP were enrolled into the AS database.

The enrolled patients with CAP contributed 7420.2 patient days at risk, with 890 patients being discharged alive. During the study, 765 patients were exposed to AS and 360 patients who were not exposed served as controls. Their baseline characteristics are presented in table 1.

The primary outcome of live discharge was observed in 79.1% of the patients (table 2).

The overall AS recommendation acceptance rate was 84.3%, with no significant difference between phase 1 (441 of 518 recommendations accepted) and phase 2 (203 of 247 recommendations accepted) ($p=0.246$). The time to AS audit and feedback was slightly earlier in phase 2 compared with phase 1 (table 3).

Over the 3-year study period, there were 11 269 total days of antimicrobial therapy, of which 4413 were administered intravenously. Compared with the control group, the mean total DOT=12.12 (SD 7.98), and the mean total DOT for phases 1 and 2 were 10.30 (SD 5.85) and 9.00 (SD 5.25) ($\chi^2(68)=106.08, p=0.002$), respectively. After controlling for confounding, the mean reduction in total DOT in phases 1 and 2 was 0.8 days (95% CI 0.7 to 0.9) and 0.71 days (95% CI 0.62 to 0.81), respectively, compared with the control group. Almost all these reductions were due to shorter courses of intravenous antimicrobials, with a mean reduction in intravenous DOT in phases 1 and 2 being 0.63 days (95% CI 0.51 to 0.78) and 0.73 days (95% CI 0.58 to 0.91), respectively. There were no differences in the mean reductions between phases 1 and 2 in either total DOT or intravenous DOT after accounting for confounding.

After accounting for selection bias and other confounding variables, the SHR for the average AS intervention effect was 1.194 (95% CI 1.014 to 1.405) (table 4). There was no improvement in either AIC or BIC when AS exposure interaction terms with either total days of intravenous therapy (SHR 1.003, 95% CI 0.961 to 1.048) or AS recommendation rejected (SHR 1.078, 95% CI 0.823 to 1.413) were tested, so these were not included in the final model.

The cumulative incidence functions for hospital discharge in AS-exposed and non-exposed patients demonstrated a reduction in the median LOS of approximately 0.5 days in AS-exposed patients (figure 2).

There was no difference in average AS intervention effect between phases 1 and 2 (SHR phase 2/phase 1=1.111 (95% CI 0.846 to 1.460)). However, the proportion of patients with CAP audited in phase 1 (518/640) exceeded the proportion audited in phase 2 (247/367) ($p<0.001$).

Table 1 Baseline characteristics of AS-exposed and non-exposed patients

Variable	AS exposure		p Value
	No (n=360)	Yes (n=765)	
Age group			p=0.467
<20	3	4	
20–39	6	10	
30–39	10	22	
40–49	16	33	
50–59	41	57	
60–69	65	157	
70–79	77	170	
80–89	94	223	
90–99	45	87	
≥100	3	2	
Sex			p=0.163
Male	168	390	
Female	192	375	
Charlson Comorbidity Score	1.68 (SD 1.85)	1.74 (SD 1.76)	p=0.61
CURB-65 score	1.82 (SD 1.17)	2.02 (SD 1.13)	p<0.01
CAP criteria			p=0.082
Yes	131	320	
No	229	445	
Empirical intravenous antibiotics			p<0.01
Yes	284	654	
No	76	111	
Ward			p<0.001
3GA	152	469	
3GC	43	112	
3SA	33	61	
4GC	69	122	
ER	64	0	
Day of week			p=0.595
Sunday	40	104	
Monday	55	109	
Tuesday	57	117	
Wednesday	60	104	
Thursday	54	122	
Friday	50	96	
Saturday	44	113	
Propensity score	0.657 (SD 0.100)	0.691 (SD 0.074)	p<0.001

AS, antimicrobial stewardship; CAP, community-acquired pneumonia; CURB 65, presence of Confusion, elevated Urea, elevated Respiratory rate, low Blood pressure and age ≥65 years; ER, emergency room.

LESSONS AND LIMITATIONS

In this study, an AS daily prospective audit and feedback intervention decreased the LOS (increased the probability of hospital discharge) in patients with CAP by an average of 19.4%, resulting in a decreased LOS by 0.5

Table 2 Outcomes of patients with community-acquired pneumonia

Outcome	Antimicrobial stewardship exposure		p Value
	No (n=360)	Yes (n=765)	
Live discharge	292	598	p=0.014
Censored	31	109	
Death	20	41	
Intensive care unit admission	13	15	
Transfer to another acute care hospital	4	2	

days regardless if the AS intervention was delivered by an AS-dedicated, ID-trained pharmacist/physician, or non-AS-dedicated, ward-based pharmacist with access to dedicated AS staff. However, 13.6% (95% CI 7.9% to 19.3%) fewer patients with CAP were exposed to AS in phase 2, suggesting that AS interventions that rely on non-dedicated AS personnel may be just as effective for common ID syndromes with well-established diagnostic and treatment guidelines as AS programme with dedicated and/or AS-trained staff, but that fewer patients will likely benefit due to the competing clinical priorities of ward-based pharmacists. The mediator(s) for this observed reduction in LOS is unclear even though it might be tempting to associate this shorter LOS to the AS intervention-mediated reduction in intravenous DOT in both phases 1 and 2. Our observed reduction in LOS compares favourably with a recent Cochrane review that determined AS interventions *probably* reduce LOS by 1.12 days (95% CI 0.7 to 1.54), although this was not solely observed in patients with CAP.¹⁰

Previously, we had estimated that our 2-year stepped-wedge observational study should have been able to detect an AS intervention effect exceeding a 20% reduction in LOS.^{2,3} The sample size calculation used for that

Table 3 Time-varying variables

Variable	AS exposure		p Value
	No (n=360)	Yes (n=765)	
Time to clinical stability (days)	3.54 (SD 3.34)	4.75 (SD 3.80)	p<0.001
Time to oral intake (days)	2.14 (SD 2.06)	2.39 (SD 1.90)	p=0.054
	Phase 1 (n=517)	Phase 2 (n=248)	
Time to AS intervention (days)	2.87 (SD 1.11)	2.59 (SD 1.67)	p=0.016

AS, antimicrobial stewardship.

Table 4 Estimation of SHRs from competing risks survival regression analysis

Variable	SHR	95% CI	
		Lower limit	Upper limit
AS intervention (compared with no AS intervention)	1.194	1.014	1.405
Secular trend by ward and month (compared with ER)			
3GA	1.010	1.001	1.018
3GC	0.995	0.988	1.002
3SA	0.998	0.994	1.001
4GC	0.997	0.995	1.000
Age group (for each decile group above <20 baseline comparator)	0.939	0.880	1.002
Sex (compared with female)	0.807	0.689	0.949
Charlson Comorbidity Score (for every one unit increase in score)	0.956	0.910	1.005
CURB-65 score (for every one unit increase in score)	0.889	0.816	0.969
CAP criteria (compared with no)	1.040	0.876	1.233
Complicated CAP (compared with no)	0.702	0.567	0.870
Total days of intravenous therapy (for every extra 1 day of antibiotic)	0.947	0.925	0.969
Time to clinical stability (for every extra 1 day)	0.990	0.987	0.994
Time to oral intake (for every extra 1 day)	0.985	0.978	0.992

AS, antimicrobial stewardship; CAP, community-acquired pneumonia; CURB-65, presence of Confusion, elevated Urea, elevated Respiratory rate, low Blood pressure and age ≥65 years; ER, emergency room; SHR, subhazard ratio.

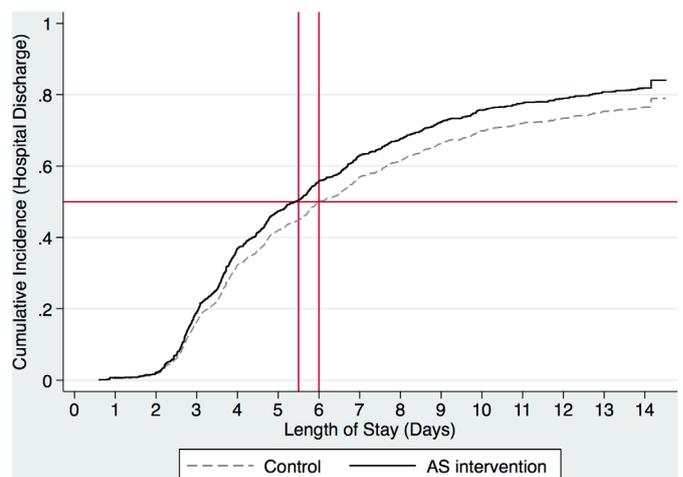


Figure 2 Cumulative incidence functions for live hospital discharge in AS-exposed and non-exposed patients. AS, antimicrobial stewardship.

study might not have sufficiently accounted for the loss of power due to clustering both within wards and within similar time periods across wards given the cross-sectional nature of the study design.²¹ The extension of that study by 1 year not only permitted us to evaluate the impact of the transition between two different AS pharmacy models, but likely provided us with a large enough sample size to detect a difference in that a priori-established primary outcome.

To the best of our knowledge, this is the only observational study of AS intervention effects in CAP that has accounted for time-dependent bias. AS interventions are generally episodic, usually occurring at different times in patients' hospital admissions. AS interventions need to be modelled as time-varying covariates in the final statistical model, otherwise the result will be to reduce the hazard rate in the exposed group and increase the hazard rate in the unexposed group culminating in a biased effect estimate.²² For our study, this time-dependent bias could lead to a false-negative SHR, meaning that we would underestimate the AS intervention effect on LOS, and possibly conclude that our AS programme had no effect on this primary outcome.

Another strength of our study included the use of a 'doubly robust' model specification for both exposure and outcome. By using this approach we reduced the risk of a biased effect estimate, and it also permitted us to estimate the causal AS intervention effect from this observational study.¹⁸ However, like all observational studies, there always exists the possibility of unmeasured confounders that are not directly related to the included variables in the model, leading to misspecification and biased effect estimates. In addition, the results from this single-site study may not be relevant to other AS programmes.

CONCLUSIONS

While AS has been deemed a required organisational practice for Canadian hospitals, there appears to be a significant heterogeneity in the structures, processes and outcomes used and measured by the different AS programmes. This may simply be a reflection of AS programmes focusing on local issues and needs. Regardless, local AS programmes should be involved in research to ensure their approach to improving patient safety and quality of care is effective. With this in mind, we have undertaken this study to evaluate the impact of a change in the structure of our hospital's AS programme on an important patient and healthcare system outcome. Our results suggest that our prospective audit and feedback intervention reduces the LOS of patients admitted to hospital with CAP, and that this benefit has not been compromised by the transition from a dedicated ID-trained pharmacist AS model to a non-dedicated, ward-based pharmacist AS model. While the observed downside of this structural change appears to be that fewer patients are exposed to the AS intervention, we

did not measure whether other ward-based pharmacy responsibilities were compromised as a result of this new responsibility. In addition, the ward-based pharmacists still had full access to the dedicated AS team members, so it is not clear whether an AS model that exclusively uses non-dedicated personnel will be able to realise the same benefits. Also, the non-dedicated personnel assumed responsibility for a programme that had already been implemented for a period of almost 2 years, further adding to the uncertainty of benefit for an AS programme that begins with non-dedicated personnel.

Competing interests None declared.

Ethics approval This study received approval from the Royal Victoria Regional Health Centre Research Ethics Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Unpublished data may be available upon request to the corresponding author.

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