Eur J Clin Microbiol Infect Dis (2012) 31:1819–1831
DOI 10.1007/s10096-011-1507-4

ARTICLE

Audit of antibiotic duration of therapy, appropriateness and outcome in patients with nosocomial pneumonia following the removal of an automatic stop-date policy

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Received: 12 September 2011 / Accepted: 29 November 2011 / Published online: 11 January 2012

Abstract Automatic stop-orders (ASOs) have been utilized to discourage inappropriately prolonged antibiotic therapy. An ASO policy, which required reordering of antibiotics after 7 days of therapy, had been in place at our institution prior to 2002, but was revoked after instances of compromised patient care due to inadvertent and inappropriate interruption of antimicrobial treatment. The objective of this study was to evaluate the impact of revoking the ASO policy on the duration of antibiotic therapy, infection-related outcome (cure vs failure), relapsing infection, occurrence of resistant bacteria and superinfection in patients with nosocomial pneumonia. A retrospective chart review of adult patients (≥ 18 years old) admitted to Sunnybrook Health Sciences Centre with nosocomial pneumonia requiring antibiotic therapy was conducted. Duration of antibiotic therapy, infection-related outcome (cure vs failure), rate of relapsing infection, resistant organisms and superinfection were determined for each cohort. Forty-two eligible adults with nosocomial pneumonia per cohort were included. Duration of antibiotic therapy was not significantly different in the pre- (11.4±3.8 days) compared with the post-ASO revocation cohort (10.8±4.1 days; $p=0.43$). There were also no significant differences between the cohorts with regard to infection-related outcome (cure vs failure), relapsing infection, or the occurrence of resistant bacteria or superinfection ($p>0.5$). Revocation of the ASO policy for antibiotics at our institution was not associated with a longer duration of antibiotic therapy, or increased incidence of infection-related mortality, relapsing infection, resistant bacteria or superinfection for patients with nosocomial pneumonia.

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Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are important causes of morbidity and mortality in Canada [1]. HAP is the second most common cause of hospital-acquired infection and is associated with higher mortality than any other nosocomial infection [1]. HAP accounts for 31% of all nosocomial infections, affecting 0.5 to 2.0% of all hospital inpatients [2], and has an attributable mortality of between 33 and 55% [3]. Appropriate antimicrobial therapy includes selection of the correct antibiotic(s), and use of appropriate dose and duration of therapy [1, 4]. Therefore, therapy of insufficient duration may

contribute to mortality in patients with nosocomial pneumonia [1, 4].

The 1995 American Thoracic Society guidelines for the management of HAP in adults did not recommend an optimal duration of antibiotic therapy [5]. They suggested that the duration should be based on each individual's response to therapy, depending on the severity of the illness, rate of response and infecting organism. Traditionally, patients received antibiotics for 10 to 14 days while those infected with non-sugar fermenting gram-negative organisms (such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.) were treated for 14–21 days [1, 6–8]. Current clinical practice guidelines recommend 7 or 8 days of antibiotic therapy as the shortest duration of therapy for HAP, including VAP, with consideration for extending therapy based on clinical response or for pneumonia due to non-sugar fermenting aerobic gram-negative bacteria and *Staphylococcus aureus* [1, 9, 10]. The potential benefits of a shorter duration of therapy are a reduction in overall antibiotic use, resistance rates, risk of superinfection and drug costs [4, 11]. Conversely, prolonged antimicrobial therapy may select for resistant pathogens in an individual and at an institutional level over time, or may cause superinfection, most notably *Clostridium difficile* colitis [4, 12].

Automatic stop-order (ASO) or automatic stop-date policies exist at many institutions as antimicrobial stewardship initiatives intended to reduce the likelihood that the duration of antibiotic therapy will be excessively prolonged, thereby potentially reducing the risk of antibiotic resistance, superinfection and drug costs [4, 13–16]. ASOs may assist in ensuring that physicians and pharmacists regularly review prescriptions that do not have a specified duration for the purpose of preventing inappropriately prolonged therapy [15]. However, use of an ASO policy requires effective communication among members of the health care team to ensure that the policy does not cause more harm than good. If antibiotic therapy is to be automatically stopped because of an ASO policy, the physician must be notified of the need to reassess the patient's therapy and to reorder the medication if continued therapy is deemed necessary. If nursing and/or pharmacy staff are unable to notify the physician, or if the notice is not acted upon, then early or inadvertent discontinuation of antimicrobial therapy will occur and this may adversely impact on patient outcome and presents a patient safety issue [15, 17, 18]. ASOs are usually designed to automatically terminate therapy after a standard duration (e.g. 7 days) and therefore, application of an ASO may be inappropriate in certain clinical situations in which prolonged antibiotic therapy is required (for example, endocarditis) [17, 19, 20]. At our institution, an automatic stop-date of 7 days was pre-defined for antibiotics and opioids in the pharmacy order-entry system. This stop-date was selected for convenience and attached to all antibiotics irrespective of type of infection, unless a physician specifically wrote for a longer or shorter duration, in which case the ASO stop-date would not apply.

There are currently limited data in the literature assessing the impact of revocation of an ASO policy on patient outcome; however, there are some reports of adverse consequences of an ASO policy. Cleary et al. reported that the use of an ASO policy for antibiotics at a tertiary-care teaching hospital was associated with undesired discontinuations of antibiotics. In 1 year, six antibiotic treatment failures were identified in 5 patients [20]. In 5 of the failures, the ASO notices to be given to physicians were not properly communicated and in the sixth failure, the physician did not know about the ASO policy [20]. The authors suggest that inadvertent discontinuation of therapy led to prolonged duration of hospitalization in 4 patients, possibly contributed to the demise of 1 patient and had no adverse consequence in 1 patient [20]. Based on their findings, it was recommended that the ASO policy be revoked at their institution. The investigation by Cleary et al. did not assess efficacy, occurrence of resistant bacteria and/or superinfection in any specific patient population before and after the revocation of their ASO. Our study attempts to fill in these gaps in the literature by evaluating these outcomes in patients with nosocomial pneumonia after having removed the ASO policy at our institution.

At our institution, a tertiary-care teaching hospital, an ASO policy had been in place since 1986. The policy automatically discontinued antibiotic therapy after 7 days for all antibiotics. A notice listing all expiring antibiotic orders was posted on the patient care unit 48 h prior to the expiry time of the orders. Antibiotic therapy was allowed to lapse at the time of order expiry, if the physician had not given orders to continue therapy. In response to incidents in which patient care was compromised by automatic discontinuation of antibiotic therapy, the ASO policy was revoked in 2002. In the absence of the ASO policy, antibiotic orders that do not specify duration of therapy could theoretically be continued until the patient's discharge. When the ASO policy was revoked, it was proposed that the inpatient pharmacists would be responsible for monitoring the duration of antibiotic therapy to ensure that treatment is not prolonged inappropriately. The impact of revoking the ASO policy on patients at our hospital was not known. As a result, the Pharmacy and Therapeutics Committee at our institution required an audit of antibiotic treatment duration post-policy revocation to be performed and compared with pre-policy revocation data to determine the extent of any adverse consequences of the policy change.

The objective of this study was to evaluate the impact of revoking the ASO policy on duration of antibiotic therapy, infection-related outcome (cure vs failure), and occurrence of relapsing infection, resistant bacteria and superinfection in patients with nosocomial pneumonia.

Materials and methods

Ethics

The study was approved by the hospital's Research Ethics Board on 21 January 2010.

Patient eligibility

Adult patients (≥ 18 years old) admitted to acute care medical wards at Sunnybrook Health Sciences Centre sequentially before 1 January 2002 or sequentially after 31 December 2002 with the diagnosis of nosocomial pneumonia (HAP, VAP or healthcare-associated pneumonia (HCAP)) who received antibiotic therapy were eligible for this study. A patient was considered to have HAP, VAP or HCAP if there was indication that the medical team had suspicion of a pneumonia-related infection and started antibiotic therapy targeted at treating a pneumonia episode. The method of data collection was chosen to capture patients a minimum of 3 months before the policy was revoked and a minimum of 9 months after it was revoked to avoid the "cross over" effect that knowledge about the policy or of its impending revocation may have had on clinical practice. Thus, the data collected should reflect standard care during the existence of the stop-date policy and after its revocation. Patients that received antibiotics completely in one of the intensive care units (including critical care, cardiovascular ICU, coronary care unit, neurosurgical ICU and the burn unit) were excluded from the study, since these units may not have followed the automatic stop-order policy that was in existence prior to 2002, and therefore, may have biased our results. If a patient was diagnosed and began treatment for pneumonia in an ICU, they were included in the study only if they were subsequently transferred to the ward and had their antibiotics continued for at least 24 h.

Study design

A retrospective chart review of 46 eligible nosocomial pneumonia patients per cohort was conducted. Eligible patients were identified for each of the respective cohorts by Health Data Records using revision 9 of the International Classification of Diseases codes (ICD-9) for post-admission pneumonia for charts before 1 January 2002 (480.0–480.9, 481, 482.0–482.9, 483.0–483.8, 484.1–484.8, 485, 486, 487, 997.3), and revision 10 (ICD-10) codes for post-admission pneumonia for charts after 31 December 2002 (J10.0, J13, J14, J15.0–J15.9, J16.0–J16.8, J17.0–J17.8, J18.0–J18.9, J84.1, J.84.9, J85.1, J85.88, T.81.80, J95.88, Y83). The order of the chart retrieval was based on when the patient was discharged. All charts retrieved by Health Data Records were reviewed sequentially back in time from 1 January 2002 and sequentially forward in time from 31 December 2002 until a total of 46 eligible patients had been reviewed for each cohort. Patient charts were reviewed for inclusion into the study in the order that they were received by Health Data Records and all episodes of pneumonia during a patient's hospital admission were included.

Sample size calculation

In this study, we reviewed patients with HAP, VAP or HCAP for appropriateness of duration of therapy and clinical outcome. Appropriateness of duration of therapy was based on current guidelines for the treatment of nosocomial pneumonia. A sample size of 46 patients was required to detect a clinically important difference of 2 days of antibiotic therapy as being statistically significant, with a power of 80% and an alpha value of 0.05.

Data collection

Data collected for review are listed in Appendix A. If a patient received an antibiotic that covered the infecting organism, but it was not intended for the treatment of pneumonia (e.g. perioperative cefazolin), then the duration of that antibiotic was not used in calculating the total duration of therapy for that episode of pneumonia, in order to determine the most accurate duration of antibiotic therapy for the episode of pneumonia. To assess severity of illness at the time of nosocomial pneumonia diagnosis, parameters from the clinical pulmonary infection score (CPIS) as defined by Singh et al. were used as representative parameters, along with the patient's worst vitals within 48 h of starting antibiotics [11]. The CPIS is a diagnostic algorithm that is suggested in guidelines for both HAP and VAP [1]. The actual CPIS could not be used in this study because many patients developed pneumonia on the ward and therefore data were lacking for many of the CPIS parameters, precluding calculation of the score for all patients. Also tabulated, were the number of cases in which the ASO was able to take effect. If the ASO did not take effect or if the drug was discontinued early, then the reason for early discontinuation was documented as either physician directed, as a result of culture and susceptibility or owing to IV to oral step-down. If a drug had a discontinuation order written on day 6, 7 or 8 of antibiotic therapy, then it was assumed that the ASO took effect. If a drug was ordered and there was never a discontinuation order, it was assumed that ASO took place at day 7 of antibiotic therapy based on confirmation with the medication administration records and/or electronic patient record pharmacy profile. If a value was unknown or not available, it was categorised as "No" or "None". This applied to patient demographic characteristics (e.g. presence of cardiovascular disease, underlying malignancy, recent surgery, chronic lung disease, organ dysfunction, admission

to hospital or nursing home in the past 3 months, and antibiotic therapy in the past 3 months (Table 1).

Statistics

Each episode of pneumonia that a patient had during their hospital admission was reviewed. An unpaired *t* test or Fisher's exact test was used to compare the pre- and post-policy cohorts for interval (e.g. age, days of antibiotic therapy) and nominal data (e.g. gender, clinical outcome, frequency of microbiological isolates, antimicrobials used), respectively. Multiple regression analysis and propensity score adjustment were completed to adjust for imbalances between groups. A p value <0.05 was considered statistically significant. The mean, standard deviation and range for continuous data were calculated.

Results

A total of 92 patients diagnosed with nosocomial pneumonia were included in the study. Forty-six patients were included sequentially prior to 1 January 2002 and 46 patients were included sequentially after 31 December 2002 to form the pre- and post-revocation of the ASO policy cohorts. The pre-cohort group included patients admitted to Sunnybrook from 2 February 2000 to 31 December 2001. The post-cohort group included patients admitted to Sunnybrook from 1 January 2002 to 8 May 2003.

Each episode of pneumonia during a patient's admission was included, providing a total of 50 episodes of nosocomial pneumonia diagnosed and treated in each cohort. Each episode of pneumonia was reviewed separately for data collection (duration of therapy and outcome parameters). Patient characteristics in each cohort are presented in Table 1. There were significant differences in the number of HAP and VAP episodes between the two cohorts; however, there were no differences in the number of episodes of HCAP (Table 1).

Cultures

There were significantly more positive sputum cultures in the pre-period than in the post-period (Table 2). However, there were no differences in the frequency of any individual species of microbial organisms or classes of organisms from sputum cultures between the pre- and post-periods (Table 2). Blood cultures and concurrent infections were also reviewed in order to determine if differences may have affected antibiotic duration of therapy for pneumonia in either cohort. There was no significant difference in rates of bacteraemia, types of concurrent infections or species of pathogens cultured between the pre- and post-periods (Table 2). In patients with concurrent infection, the incidence of gram-positive infection was significantly higher in the pre-period and the incidence of gram-negative infection was significantly higher in the post-period. However, importantly, there was no difference in the incidence of *S. aureus* or *P. aeruginosa* infections between the pre- and post-periods to potentially confound our results, since a longer duration of therapy may be associated with either of these organisms. Thus, the existence of other infections in our patients can be ruled out as a potential confounding factor of the duration of therapy determined in this study.

Antibiotic selection and duration of antibiotic therapy

For the most part, antibiotic selection frequency was not significantly different in the pre- and post-period cohorts (Table 3); the notable exceptions were a significantly greater use of cloxacillin and co-trimoxazole in the pre-period cohort and levofloxacin in the post-period cohort. This change in antibiotic selection was likely a reflection of the addition of levofloxacin to our hospital formulary in 2000, and published evidence supporting the use of levofloxacin in HAP in February 2003, which resulted in levofloxacin becoming our most frequently used single agent for HAP in 2003 [21, 22]. However, the shift in antimicrobial selection would not be expected to affect duration of therapy. Duration of antibiotic therapy was not significantly different between the two cohorts (Table 4) using the unadjusted data. To account for differences in documented parameters between the two cohorts, multiple regression analysis followed by propensity score adjustment were conducted. The propensity score adjusted results also indicate that duration of therapy was not significantly different between the two cohorts (Table 4).

Our current institutional pneumonia treatment guidelines recommend 7–8 days of antibiotic therapy for a given episode of nosocomial pneumonia (with 14–21 days considered appropriate if the infecting organism is a non-sugar fermenting bacteria or *S. aureus*, based on clinical resolution). The data show that patients at our institution received this duration of antibiotic therapy 30% of the time in both cohorts ($p>0.05$).

Patient outcome

Prior to revocation of the ASO policy, all patients included in the chart review survived their episode(s) of pneumonia. After revoking the policy, 7 patients failed therapy and

Table 1 Patient characteristics

Characteristics[a, b]	Pre-period number (%)	Post-period number (%)	*p* value[k]
Age (years)[c]	66.4±17.0 (19–85)	74.7±14.0 (33–96)	0.012
Gender			
Males	34 (74)	25 (54)	0.081
Comorbidities	45 (98)	45 (98)	1.50
Cardiovascular disease	30 (65)	32 (70)	0.82
Underlying malignancy	9 (20)	19 (41)	0.04
Recent surgery[d]	39 (85)	30 (65)	0.053
Respiratory failure[e]	37 (80)	17 (37)	< 0.0001
Chronic lung disease	11 (24)	7 (15)	0.43
Organ dysfunction[f]	12 (26)	10 (22)	0.81
Admission to a hospital or nursing home in the past 3 months	19 (41)	20 (43)	0.91
Antibiotic therapy in the past 3 months	42 (91)	33 (72)	0.063
Nursing unit and service at time of admission			
ICU	38 (83)	18 (39)	<0.0001
Ward	8 (17)	28 (61)	
Nursing unit during HAP episode			
ICU	22 (48)	12 (26)	0.051
Ward	24 (52)	34 (74)	
Length of hospital stay (days)[c]	33±28 (5–140)	29.2±23.7 (4–107)	0.46
Intubated or in critical care during the given hospital stay before time of pneumonia diagnosis	45 (90)	25 (50)	< 0.0001
ICU stay at any point during antibiotic therapy	17 (34)	14 (28)	0.67
ARDS[g] (*n*=46)	4 (7)	1 (2)	0.36
Worst vitals within 48 h of starting antibiotics:			
Temperature (°C)[c]	37.7±0.7 (36.0–39.2)	37.5±0.9 (36–40)	0.32
Blood leukocytes ($\times 10^9$/L)[c]	12.9±4.7 (4.5–23.3)	12.9±5.4 (2.6–31.6)	0.96
Blood pressure (mmHg)[c]			
SBP	106.1±15.8 (50–138)	110.8±16.4 (82–140)	0.16
DBP	57.4±13.0 (30–90)	58.8±13.1 (35–80)	0.61
Respiratory rate (breaths/min)[c]	26.3±7.1 (11–44)	27.0±7.4 (18–48)	0.68
Heart rate (beats/min)[c]	110.9±20.8 (75–155)	106.2±18.9 (59–140)	0.25
Tracheal secretions[h]			
None or non-purulent	20 (41)	33 (67)	0.015
Purulent	29 (59)	16 (33)	
Description of culture[i]			
Light to moderate	28 (45)	11 (55)	0.61
Heavy	34 (55)	9 (45)	
Pulmonary radiography[j]			
Normal	26 (54)	15 (31)	0.038
Abnormal	22 (46)	33 (69)	

Table 1 (continued)

Characteristics[a, b]	Pre-period number (%)	Post-period number (%)	*p* value[k]
Number of HAP episodes	17 (34)	29 (58)	0.027
Number of VAP episodes	21 (42)	2 (4)	< 0.0001
Number of HCAP episodes	12 (24)	19 (38)	0.19

SBP=systolic blood pressure; DBP=diastolic blood pressure

[a] n=46 patients for patient characteristics: "Age" to "Length of hospital stay"

[b] n=50 episodes of pneumonia for patient characteristics: "Intubated or in critical care before time of pneumonia diagnosis" to "Number of HCAP episodes"

[c] Mean±SD (range). Temperature data missing for 1 episode of pneumonia in the pre-period and for 2 episodes in the post-period. Blood leukocyte value missing for 13 episodes in the pre-period and 10 episodes in the post-period. Blood pressure data were missing for 2 patients in the pre-period and for 1 patient in the post-period. Respiratory rate and heart rate values were missing for 2 episodes in the pre-period and 1 episode in the post-period

[d] Within the previous 3 months

[e] Respiratory failure was defined as having been intubated during the given hospital stay prior to the pneumonia episode(s)

[f] Renal or hepatic

[g] Acute respiratory distress syndrome (ARDS) during the given hospital stay, prior to the pneumonia episode(s)

[h] Tracheal secretion data were missing for 2 patients in the pre-period (n=48 episodes) and for 1 patient in the post-period (n=49 episodes)

[i] Pre-period=62 positive cultures, post-period=20 positive cultures

[j] n=48 episodes in pre and post-cohorts. 2 patients in each group did not undergo a chest x-ray

[k] $p<0.05$ statistically significant

passed away during or within a week of antibiotic therapy (p=0.012) and 5 of these deaths were a result of infection (Table 5). Table 6 lists the characteristics of the 7 patients in whom therapy failed.

There were no significant differences in infection-related outcome (cure vs failure), occurrence of relapse of infection with the same organism or a resistant pathogen (no cases in either cohort), or occurrence of superinfection ($p>0.05$; Tables 2, 5).

Discussion

Automatic stop-orders (ASOs) were an early antimicrobial stewardship initiative commonly utilized to discourage inappropriately prolonged antibiotic therapy. At Sunnybrook Health Sciences Centre, an ASO policy had been in place for 16 years prior to 2002, but was revoked after incidents of compromised patient care following inadvertent and inappropriate interruption of antimicrobial treatment. Currently, published studies examining the outcome of removing an ASO policy are lacking. The single published study that looked at the impact of removing an ASO policy did not assess outcomes such as infection-related mortality, occurrence of resistant bacteria and/or occurrence of superinfection between patients before and after the removal of an ASO policy in any specific patient population [20]. Thus, our study helps to fill these gaps in the literature using nosocomial pneumonia as the prototype infection.

The major concern with revocation of the ASO policy at our institution was that this would consequently lead to unacceptably long durations of antibiotic therapy. The results of our study show that removal of the ASO policy did not result in an increase in the overall duration of antibiotic therapy for a given episode of nosocomial pneumonia. It also did not have any significant effect on infection-related outcome (cure vs failure), occurrence of relapse of infection, development of resistant organisms or superinfection.

Nosocomial pneumonia was chosen as the prototype infection because it is an infection that is associated with significant mortality when treated inappropriately and there are recommendations to guide duration of therapy to attain positive clinical outcome and minimize the risk of resistance and superinfection. The objective of this study was to evaluate the impact of revoking the ASO policy on duration of antibiotic therapy, infection-related outcome (cure vs failure), and occurrence of relapsing infection, resistant bacteria and superinfection in patients with nosocomial pneumonia. Therefore, we wanted to assess the impact of revoking ASO on each of these parameters, recognizing that mortality might be higher in critically ill patients or those with comorbidities. The recommended duration of therapy for nosocomial pneumonia, regardless of subgroups, is the same according to current published guidelines (acknowledging that longer durations of therapy may be appropriate for *S. aureus* and *Pseudomonas aeruginosa*) [1, 9, 10]. Propensity scoring was used to adjust for significant differences

Table 2 Microbiology results

Parameter	Pre-period[e] number (%)	Post-period[e] number (%)	*p* value[g]
Sputum[a]			
Positive cultures	47[f] (94)	15[f] (30)	< 0.0001
Total isolates	62	20	
Microorganism—classes			
Gram-positives	14 (23)	8 (40)	0.15
Gram-negatives	46 (74)	11(55)	0.16
Fungal	2 (3)	1(5)	1.00
Microorganism—species			
Methicillin-sensitive S. aureus (MSSA)	13	6	0.54
Methicillin-resistant S. aureus (MRSA)	1	0	1.00
Enterobacter	6	0	0.33
Leclercia	1	0	1.00
Hafnia alvei	2	0	1.00
Candida	2	1	1.00
Serratia	5	2	1.00
Pseudomonas	7	2	1.00
Haemophilus influenza BL−	6	2	1.00
H. influenza BL+	1	1	0.43
Escherichia coli	4	3	0.35
Moraxella catarrhalis BL+	1	0	1.00
Klebsiella	9	1	0.44
Morganella morganii	1	0	1.00
Citrobacter	1	0	1.00
Proteus mirabilis	2	0	1.00
Streptococcus pneumoniae	0	2	0.057
Blood[b]			
Positive cultures	6[f] (12)	4[f] (8)	0.74
Total isolates	6	6	
Microorganism—classes			
Gram-positives	3 (50)	1(17)	0.55
Gram-negatives	3 (50)	5 (83)	0.55
Microorganism—species			
Pseudomonas	1	0	1.00
Coagulase negative staphylococci (CNST)	2	0	0.45
Enterococcus	1	0	1.00
Klebsiella	1	1	1.54
H. influenza BL−	1	0	1.00
E. coli	0	2	0.45
Serratia	0	1	1.00
B. fragilis BL+	0	1	1.00
MRSA	0	1	1.00
Concurrent infection[c]			
Positive cultures	16[f] (32)	15[f] (30)	1.00
Total isolates	16	15	
Microorganism—classes			
Gram-positives	13 (81)	5 (33)	0.01
Gram-negatives	2 (13)	8 (53)	0.02
Fungal	1 (6)	2 (13)	0.60
Microorganism—species			
MSSA	5	2	0.22
Enterococcus	5	2	0.22
Pseudomonas	1	0	0.48
E. coli	1	4	0.33
CNST	2	1	0.60
Klebsiella	0	1	1.00
Gram-positive cocci (unspecified)	1	0	0.48
Gram-negative bacilli (unspecified)	0	0	–
Candida	1	1	1.00
Yeast	0	1	1.00
C. difficile negative	0	3	0.23
Superinfection[d]			
Occurrence of superinfection	9[f] (18)	4[f] (8)	0.23
Total isolates	12	3	
Microorganism—classes			
Gram-positives	3 (25)	1 (33)	1.00
Gram-negatives	8 (67)	2 (67)	1.00
Fungal	1 (8)	0	1.00
Microorganism—species			
Pseudomonas	2	0	1.00
Acinetobacter baumanii	1	0	1.00
CNST	1	0	1.00
Enterococcus	2	0	1.00
Enterobacter	1	0	1.00
C. difficile positive	2	1	0.52
Leclercia	1	0	1.00
Hafnia alvei	1	0	1.00
Candida	1	0	1.00
E. coli	0	1	0.20
S. pneumoniae	0	1	0.20

BL+ = beta lactamase producing, BL- = non-beta lactamase producing

[a] More than one organism could have been cultured for a given sputum specimen

[b] More than one organism could have been cultured for a given blood specimen

[c] More than one organism could have been cultured for a given concurrent infection. There were no significant differences in the types of concurrent infections that arose

[d] More than one organism could have been cultured for a given superinfection. There were no significant differences in the types of superinfections that arose

[e] $N=50$ episodes of pneumonia for the pre -and post-period cohorts

[f] Number of episodes of pneumonia with a positive culture

[g] $p<0.05$ statistically significant

Table 3 Antibiotics used for the treatment of pneumonia

Antibiotic prescribed for an episode of pneumonia	Pre-cohort frequency N=93 (%)[a]	Post-cohort frequency N=61 (%)	p value
Amoxicillin	1 (1)	0 (0)	1
Ampicillin	2 (2)	0 (0)	0.52
Azithromycin	1 (1)	5 (8)	0.036
Cefazolin	7 (7)	6 (10)	0.77
Ceftazidime	6 (6)	2 (3)	0.48
Ceftriaxone	12 (13)	8 (13)	1
Cefuroxime	10 (11)	2 (3)	0.13
Cephalexin	2 (2)	1 (2)	1
Ciprofloxacin	14 (15)	8 (13)	0.82
Clindamycin	3 (3)	1 (2)	1
Cloxacillin	10 (11)	0 (0)	0.0064
Co-trimoxazole	10 (11)	0 (0)	0.0064
Erythromycin	1 (1)	0 (0)	1
Gentamicin	2 (2)	1 (2)	1
Levofloxacin	1 (1)	21 (34)	<0.0001
Metronidazole	1 (1)	3 (5)	0.3
Piperacillin	3 (3)	0 (0)	0.28
Tobramycin	4 (4)	0 (0)	0.15
Vancomycin	3 (3)	3 (5)	0.68

[a]The percentages total 98% owing to the rounding of individual frequencies

in patient characteristics (e.g. age, comorbidities and ICU vs ward patients) between the pre- and post-period cohorts, which could themselves have an impact on the outcomes of interest in this study (duration of therapy, infection-related outcome, relapsing infection, resistant bacteria and superinfection), to enable an appropriate assessment of the impact of ASO revocation on the outcomes of interest. Current guidelines recommend 7–8 days of therapy for most patients, which is a duration that allows for observing prolonged duration of therapy after removal of the ASO policy. Other infections such as osteomyelitis and endocarditis, which have treatment regimens that are appropriately long, were excluded from our review because they may have biased against seeing any real differences in duration of therapy after removing our ASO policy. Patients who received antibiotics completely in an intensive care unit (critical care, cardiovascular ICU, coronary care unit, neurosurgical ICU or the burn unit) were excluded from the study because of concerns that the ASO policy would not be able to take effect, since antibiotics are assessed vigilantly and stop-dates are often specified. Also, potentially appropriate

Table 4 Duration and appropriateness of antibiotic therapy

	Unadjusted			Adjusted		
Parameter	Pre-period[d]	Post-period[d]	p value[e]	Pre-period[d]	Post-period[d]	p value[e]
Overall duration of therapy(days)[a, b]	11.4±3.8 (5–22)	10.8±4.1 (4–26)	0.43	11.4±3.2 (6–19)	11.8±4.1 (5–26)	0.62
Appropriate duration of therapy based on current practices[c]	15 (30)	13 (30)	1.00			

[a] Mean (days)±SD (range)

[b] Duration of antibiotic therapy (in days) for a given episode of pneumonia, where all the organisms are covered by therapy, in surviving patients (7 deaths in the post-period were excluded)

[c] Number (%). Appropriate duration of antibiotic therapy for a given episode of pneumonia, in surviving patients (7 deaths in the post-period were excluded). This was based on recommendations to treat for 7–8 days for a given episode of pneumonia, 14–21 days for *S. aureus* or *P. aeruginosa* pneumonia

[d] Pre-period: N=50 episodes of pneumonia, post-period: N=43 episodes of pneumonia

[e] $p<0.05$ statistically significant

Table 5 Patient outcome

Parameter	Pre-period, number (%)[d]	Post-period, number (%)[d]	*p* value[e]
Infection-related outcome following complete course of antibiotic therapy for a given episode			
Survived[a]	50 (100)	45 (90)	0.0563
Died[b]	0	5 (10)	
Occurrence of superinfection[c]	9 (18)	4 (8)	0.23

[a] Survival=cure+relapse (Appendix A)

[b] Death due to pneumonia infection (failure, Appendix A)

[c] There were no differences in the types of superinfection that arose and the pathogens that were cultured

[d] N=50 episodes of pneumonia in the pre- and post-periods

[e] $p<0.05$ statistically significant

prolonged therapy in these patients would make it difficult to identify true differences in duration of therapy before and after revoking the ASO policy and would thus confound the results.

In order to assess the severity of illness at the time of diagnosis, parameters from the CPIS were utilized as an indicator of degree of illness. According to the Canadian practice guidelines, the CPIS is recommended to be used for both HAP and VAP patients to improve diagnosis of pneumonia [1]. The major limitation of using the CPIS score was that many patients included in this study were diagnosed and/or treated on the ward, and the necessary data for calculating the CPIS (ex. PO_2, FiO_2) was often absent. Thus, parameters that are used to calculate CPIS score were used as surrogate markers of the degree of illness for both the pre- and post-period cohorts, since no other tool exists for HAP patients. These parameters were collected based on data provided on the day on which the antibiotic for pneumonia was started (i.e. the day the patient was diagnosed with pneumonia). In addition, the patient's worst vitals within 48 h of starting antibiotic therapy were collected to give a full representation of the severity of their illness.

To determine overall duration of therapy, days of therapy where all the infecting organisms were covered by antibiotic therapy were included for surviving patients. Patients who died were not included in the determination of mean overall duration of therapy to eliminate bias in the calculation (0 cases in the pre-period and 7 cases in the post-period were excluded for this reason). These patients had their antibiotics discontinued early because they either died while undergoing therapy or within a week of stopping antibiotic therapy, and inclusion of their data may have biased this study against seeing a difference in treatment duration, if one had existed.

Because there were significant differences in documented parameters between the two cohorts that may have affected duration of therapy, we subsequently conducted a multiple regression analysis followed by propensity score adjustment. The propensity score adjusted result also confirmed that duration of therapy was not significantly different between the two cohorts (Table 4). This may be because physicians are being more vigilant in writing specific stop-dates for antibiotics and pharmacists are taking more responsibility for monitoring duration of antibiotic therapy and communicating with the medical team when an agent should be stopped.

In the 50 episodes of pneumonia in the pre-period, there were 93 opportunities for the ASO policy to take effect. However, the ASO took effect in only 32 cases (34%). Therefore, although there was an antibiotic stop-date policy at our institution, in approximately two thirds of these cases, the policy was not invoked, indicating that the utility of the ASO policy may have been limited. Reasons for not invoking the ASO policy included a physician order for a specific stop-date or specific duration to complete the full course of therapy, a physician order to stop or change the drug, based on culture and susceptibility results and/or a switch to oral step-down therapy, or the patient completed their course of antibiotic therapy as an outpatient.

The appropriateness of duration of the overall antibiotic therapy based on our current guidelines shows no significant difference in appropriateness between the two cohorts (30% in both the pre- and post-period cohorts, $p>0.05$; Table 4). This was assessed to see if revoking the ASO policy had affected the appropriateness of the duration of therapy based on today's guidelines. It is difficult to know, however, whether or not a specific duration of therapy was appropriate for each individual patient, because of the retrospective design of this study. Also, during the time period of this study (2001–2003), guidelines recommending 7–8 days of antibiotic therapy had not been widely adopted, which could explain the low percentage of the appropriate duration of antibiotic therapy for both cohorts based on current guidelines.

Concurrent bacteraemia or coexisting infection were noted in order to see if these infections may have contributed to longer antibiotic duration and thus affected any difference seen in the duration of therapy between the pre- and post-period cohorts. Bacteraemia rate, types of concurrent infections and infecting organisms were similar in both cohorts, and there

Table 6 Characteristics of patients in whom antibiotic therapy failed

Patient[a]	Cardiovascular disease (Yes/No)	Underlying malignancy (Yes/No)	Recent surgery[c] (Yes/No)	Respiratory failure[d] (Yes/No)	Chronic lung disease (Yes/No)	Organ system derangements[e] (Yes/No)	Ward or ICU on admission	Nursing unit during HAP episode (Ward or ICU)	ARDS[f] (Yes/No)	Intubated or in an ICU during this hospital stay before episode of pneumonia? (Yes/No)	Bacteraemia (Yes/No)	Concurrent infection (Yes/No)	Culture of pneumonia infection present (Yes/No)[j]
1	Yes	No	No	No	No	Yes	Ward	Ward	No	No	No	No	No
2[b]	Yes	Yes	No	No	Yes	No	Ward	Ward	No	No	No	Yes[h]	No
3	Yes	No	No	No	No	No	Ward	Ward	No	No	No	No	No
4	Yes	No	No	Yes	No	No	ICU	Ward	No	Yes	No	No	Yes[k]
5	No	Yes	No	No	No	No	Ward	Ward	No	No	Yes[g]	Yes[I]	No
6	Yes	No	Yes	No	No	Yes	Ward	Ward	No	No	No	No	No
7[b]	Yes	Yes	Yes	No	No	No	Ward	Ward	No	No	No	No	No

[a] Patients who died while on antibiotic therapy for their episode of pneumonia or within a week of discontinuing antibiotic therapy

[b] Patient died of causes other than their pneumonia infection (history of cancer that ultimately contributed to his/her death)

[c] Within the previous 3 months

[d] Respiratory failure was defined as having been intubated during the given hospital stay prior to the pneumonia episode(s)

[e] Renal or hepatic

[f] Acute respiratory distress syndrome (ARDS) during the given hospital stay prior to the pneumonia episode(s)

[g] *B. fragilis* bacteraemia

[h] Urinary tract infection

[I] MSSA (methicillin-sensitive *Staphylococcus aureus*) cellulitis, UTI (urinary tract infection; yeast)

[j] Yes = there were positive cultures, No = absence of positive cultures

[k] *E. coli* grew in sputum during a relapse of the patient's pneumonia

were no differences in the rates of such pathogens (Table 2). Thus, the duration of antibiotic therapy is primarily representative of the treatment of pneumonia and not another confounding infection.

One of the objectives of this study was an assessment of outcome in patients with HAP, VAP or HCAP. However, both recognised and unrecognised confounders may have existed to bias patient outcome (cure vs failure). Owing to the complexity of a patient with HAP, VAP or HCAP, many factors besides duration of therapy may affect outcome and no conclusion of causation may be made for duration of therapy and outcome. The retrospective study design along with the assumptions that the diagnosis of pneumonia was correctly made and appropriate antibiotic therapy was used may all bias the results of outcome and any association of outcome with length of therapy.

Changing infection control practices may also confound the evaluation of the occurrence of resistant pathogens in the cohorts of a retrospective study, recognising that infection control has been a hospital priority at our institution for over 20 years. New infection control or unit-specific initiatives may have been implemented in our hospital during the period of the study (2000–2003) and may have had a beneficial impact on resistance. However, owing to the complexity of managing infectious diseases in any institution, no single initiative can take either credit or blame for changes in resistance. Rather, when changes in resistance are observed, they are likely due to a combination of both infection control and antimicrobial stewardship initiatives. Regardless, the results of our study indicate that removal of our ASO policy did not have a negative impact on changes in resistance at our institution. This is further supported by the observation that duration of antibiotics did not increase, since it is increased duration of antibiotics following revocation of an ASO policy that could increase the risk of resistance.

Although a sample size of 46 subjects per cohort may be considered small and may not be able to identify a clinically important difference in infection-related outcome, resistance or superinfection as being statistically significant; the sample size was calculated as being sufficient to identify a difference in duration of antibiotic therapy of 2 days as being clinically important and statistically significant. Poor compliance with the ASO policy prior to its revocation is another limitation as it may diminish the ability to observe any significant effect seen in outcomes between the pre- and post-period cohorts.

The impact of duration of therapy on mortality relates to the concern that an inappropriately short duration of therapy may increase the risk of mortality and therefore, pose a patient safety concern with ASO policies. If therapy had been inappropriately long, then the risk to patients would have been potentially an increased risk of superinfection and/or the selection of resistant organisms (or opportunistic organisms such as *Candida*, *Enterococci*, and *C. difficile*). Understanding this, we examined the 7 deaths in the post-ASO policy cohort (Table 6). There were a total of 5 deaths attributable to infection. In 2 of these patients, pneumonia was the only source of infection at the time of antibiotic treatment, and these patients died while on antibiotic therapy. The third patient had concurrent *Bacteroides fragilis* bacteraemia along with their pneumonia infection and died while on antibiotic therapy for the two infections. Therefore, inappropriate premature discontinuation of antibiotics was not a factor in any of these 3 patients. In the remaining 2 patients, the infection resulting in death was a relapse of their original pneumonia infection. In one of these patients the duration of therapy for their previous pneumonia infection was of adequate duration (13 days). The remaining patient had MRSA bacteraemia along with pneumonia (MRSA, *Escherichia coli* and *P. aeruginosa* cultured from sputum) as their initial infection for which they received 4 weeks of vancomycin and 2 weeks of ceftazidime. This patient died after 1 day of antibiotic treatment for a relapse of their pneumonia (*E. coli* cultured from sputum). Therefore, there is no reason for concern that revoking the ASO policy resulted in inappropriately short or long durations of therapy in these patients that might have caused their deaths.

Some may argue that removal of the ASO policy showed no positive impact on clinical or microbiological outcomes; however, ASO policies are but one intervention suggested for antimicrobial stewardship, and initiation or removal of a single policy/intervention is unlikely to show beneficial effect in isolation in a complex patient population where numerous factors can affect outcome. Importantly, our study observed that removal of the ASO policy did not cause harm to patients (mortality, superinfection) or impact negatively on the hospital ecology (microbial resistance), while, most importantly, eliminating the safety risk of patients having their antibiotics discontinued prematurely (e.g. endocarditis and osteomyelitis). This is the benefit of removal of ASO policies.

We have no indication that the pharmacists' workload at our centre increased as a result of the revocation of the ASO policy. Pharmacists at our institution printed daily patient medication profiles for all active medications in both the pre- and post-period cohorts evaluated in this study. Included in these profiles are antibiotics with dose, route and duration. Today, the pharmacists can use these profiles to work with the medical team to reassess antibiotic use and order appropriate stop-dates, without the fear that an antibiotic has fallen off the list because it was inappropriately discontinued. This keeps pharmacists updated on antibiotic therapy and duration so that they can make an assessment of whether patients require a longer duration of therapy without involving too much added labour.

More recently, in addition to the liaison pharmacists' activities, an antimicrobial stewardship team was instituted to conduct prospective audit and feedback on targeted antibiotics (October 2009—level III critical care units; and November 2010—hospital medical and surgical wards). Our assessment of the ASO policy revocation was carried out during a period prior to the implementation of our new antimicrobial

stewardship programme and we did not identify a negative impact on patient outcome, resistance, superinfection or duration of therapy, while patient safety was improved. With antimicrobial stewardship becoming more widely adopted to promote the rational use of antimicrobials, it becomes clear that ASO policies are restrictive and out-dated and our study provides evidence that revoking an ASO policy does not have a negative impact on patient outcome.

Conclusion

The results of our study demonstrate that revocation of the ASO policy has not resulted in inappropriately prolonged duration of antibiotic therapy in the treatment of nosocomial pneumonia in patients at our hospital. Removal of the ASO policy did not have a negative impact on infection-related outcome, occurrence of relapse, resistant bacteria or superinfection in patients with nosocomial pneumonia. Therefore, this study did not support the use of an ASO policy as a stewardship initiative to reduce the duration of antibiotic therapy, resistance or superinfection, when nosocomial pneumonia is used as the prototype infection for the assessment.

Conflict of interest statement None.

Appendix A

Data collected from eligible patient charts, nursing flow sheets and electronic patient records for chart review included:

1. Patient demographics: age, gender, co-morbid conditions (cardiovascular disease, underlying malignancy, recent surgery, respiratory failure, chronic lung disease, organ system dysfunction, including renal and hepatic disease)
2. Nursing unit on admission and when diagnosed with pneumonia
3. Prior admission to a hospital or nursing home in the previous 3 months
4. Antibiotic therapy within 3 months of pneumonia diagnosis
5. Need for intubation or in critical care prior to the time of pneumonia diagnosis during hospital admission
6. Acute respiratory distress syndrome (ARDS) prior to diagnosis of pneumonia
7. Temperature (°C) on the first day of antibiotic therapy
8. The patient's worst vitals within 48 h of starting antibiotic therapy:
   a) Blood leukocytes ($\times 10^9$/L)
   b) Blood pressure (mmHg)
   c) Respiratory rate (breaths/min)
   d) Heart rate (beats/min)
9. Presence of tracheal secretions (purulent or non-purulent)
10. Description of the culture (light, moderate or heavy)
11. Pulmonary radiography (normal or abnormal) and progression of pulmonary infiltrates
12. Number of HAP, VAP and HCAP episodes
13. Admission to the ICU while on antibiotic therapy and/or transfer from ICU to the ward
14. Infection-related diagnosis (HAP, VAP, HCAP)
    a) Sputum culture (culture, sensitivities and description of the sample)
    b) Presence of concurrent blood infections (and their respective cultures and sensitivities)
    c) Presence of other concurrent infections (type of infection, cultures and sensitivities)
15. Duration of therapy of each antibiotic prescribed for a given episode of pneumonia (where day 1 is the day the antibiotic was prescribed and the final day of therapy is the day that the specific antibiotic was discontinued)
16. Overall duration of antibiotic therapy for the given episode of nosocomial pneumonia; includes days of therapy where all pathogens are covered for surviving patients (day 1 is the date on which the initial antibiotic was begun for the episode of nosocomial pneumonia and the final day of therapy is the date on which the last antibiotic prescribed for the episode of nosocomial pneumonia was discontinued)
17. Appropriateness of the duration of therapy based on current practice
18. Infection-related outcome following a complete course of therapy for the episode of nosocomial pneumonia was documented: cure, failure, relapse, superinfection
    a) *Cure*: resolution of infection based on survival of the patient when antibiotics were discontinued and no relapse of infection within 2 weeks
    b) *Failure*: death during antibiotic therapy for the episode of pneumonia or within a week of discontinuing therapy
    c) *Relapse*: recurrence of nosocomial pneumonia within 2 weeks of discontinuing the initial course of antibiotic therapy with the same organisms or one that is resistant to any antibiotic used to treat the initial episode of pneumonia (including the infection-related diagnosis, the bacteria cultured and the sensitivity profile)
    d) *Superinfection*: infection with a new and/or opportunistic organism within 1 week of discontinuing antibiotic therapy, including *Enterococcus*, *Clostridium difficile* and fungal pathogens (including the

infection-related diagnosis, the bacteria cultured or existence of *C. difficile* toxin, and sensitivity profile of the bacteria cultured, outcome of the secondary infection, either resistant bacteria or superinfection; cure/failure/relapse as defined above)

19. Length of hospital stay

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