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Note

Non-adherence to antimicrobial stewardship prospective audit and feedback advice: Risk factors and clinical consequences☆

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ABSTRACT

Amongst 325 patients receiving restricted antimicrobials whose management was subject to antimicrobial stewardship prospective audit and feedback, adherence to advice was 78%. Non-adherence was associated with diabetic patients, giving more than 1 piece of advice and receipt of piperacillin/tazobactam therapy, and was inversely associated with liver disease. Adherence to advice was associated with a one third reduction in duration of antimicrobial use without adversely impacting other infection-related patient outcomes.

The overuse of antimicrobials contributes to the development of resistant pathogens, limiting their usefulness. A recent Australia-wide survey found that 23% of antimicrobial prescriptions for hospitalised patients were inappropriate, demonstrating considerable scope for improvement in their use [1]. Antimicrobial stewardship (AMS) is a multifaceted intervention that aims to preserve the current and future stock of antimicrobial agents by promoting their appropriate selection, dosing, route, and duration of use. A key component of successful AMS is prospective audit and feedback (PAF) [2], which refers to the provision of unsolicited therapeutic advice for patients receiving restricted (eg. broad-spectrum) antimicrobials. Rates of adherence to PAF advice vary from 68% to 77% [3–5]. Factors associated with non-adherence to PAF advice are incompletely understood, but may include the speciality service receiving the advice [3], and the type of advice provided [5]. A better understanding of these risk factors may allow AMS services to direct their interventions accordingly. Studies examining the impact of non-adherence to PAF advice on clinical outcomes demonstrate conflicting results [4,6]. The aims of our study were to identify factors associated with non-adherence to PAF round advice, and to determine if non-adherence was associated with adverse clinical outcomes.

We performed a prospective observational cohort study on all inpatients at a 783-bed tertiary hospital in Western Australia receiving restricted antimicrobials who were referred for PAF between the 3rd of January and the 22nd of April 2017. The restricted antimicrobials included those that were broad spectrum (eg. piperacillin/tazobactam), high-cost (eg. intravenous lincosamides), or toxic (eg. vancomycin). Initiation of restricted antimicrobials outside of pre-existing local guidelines required pre-approval by an infectious diseases (ID) physician or microbiologist. PAF was provided every weekday, and involved an ID physician and ID pharmacist provided written advice to the patient's primary clinician, via the electronic medical record, with or without accompanying verbal communication.

☆ Statement: All authors meet the IMCJE authorship criteria.

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Patient, infection, and advice related variables were extracted from the patient's electronic medical record. Standard definitions for immunosuppression [7], infection classification (community onset, non-healthcare-associated, community onset, healthcare associated, or nosocomial) [8], and acute kidney injury [9] were applied. *Clostridium difficile* infection was defined as detection of *Clostridium difficile* by polymerase chain reaction from a faecal sample. Infection site was classified according to the Australian Therapeutic Guidelines [10]. PAF advice was categorised as either: discontinuation, escalation of therapy (eg. oral to intravenous switch, or to a broader spectrum agent), intravenous to oral switch, dose adjustment, advice on duration of therapy, reduced breadth of coverage (same route), no change to therapy, therapeutic drug monitoring, microbiology test advice, recommending a formal ID consult, or other advice. Patients aged less than 18 years, pregnant women, patients with insufficient information available, or those that had received prior review by an ID physician were excluded.

Adherence was assessed 48 h after PAF advice was given. Where greater than one piece of advice was provided, adherence was categorised as adherent (≥66% of advice followed) or non-adherent (<66% of advice followed).

Data were analysed using R [11] and presented as medians (inter-quartile range) or proportions. Univariate comparisons between adherence and non-adherence with PAF advice were performed using Mann-Whitney *U* and Chi-squared tests for continuous and categorical variables, respectively. Multivariate analysis was performed using backward stepwise logistic regression and the most parsimonious model was chosen using the minimum Akiake's Information Criterion after the removal of each variable. Variables were included when $P < 0.10$ on univariate regression analysis. South Metropolitan Health Service Human Research Ethics Committee approval was obtained (2016-250).

PAF advice was provided to 390 patients receiving restricted antimicrobials. Sixty five patients were excluded due to age less than 18 (n = 10), pregnancy (n = 2), insufficient information available (n = 2), and prior review by an ID physician (n = 51). Overall, clinicians were adherent to PAF advice for 253 of 325 patients (78%). Patient, infection, and advice characteristics, plus univariate analysis for determinants of and outcomes associated with non-adherence to PAF advice are provided (Table 1). Piperacillin/tazobactam was the most commonly prescribed restricted antimicrobial, accounting for nearly 60% of all AMS encounters

Table 1
Univariate analysis of risk factors for and clinical impact of non-adherence to prospective audit and feedback advice.

	Total	Adherent	Non-adherent	P-value
	n = 325	n = 253	n = 72	
Age (IQR)	66 (49–80)	66 (47–80)	68 (55–76)	0.50
Male	173 (53%)	132 (52%)	41 (57%)	0.47
Infection type				0.62
Community onset, non health care associated	177 (54%)	138 (54%)	39 (54%)	
Community onset, healthcare associated	100 (31%)	80 (32%)	20 (28%)	
Nosocomial	48 (15%)	35 (14%)	13 (18%)	
Infection site				0.19
Intra-abdominal	112 (34%)	83 (33%)	29 (40%)	
Skin and soft tissue	67 (21%)	52 (21%)	15 (21%)	
Respiratory tract	58 (18%)	42 (17%)	16 (22%)	
Urinary tract	54 (17%)	48 (19%)	6 (8%)	
Other	34 (10%)	28 (11%)	6 (8%)	
Treating team				0.32
Medical	107 (33%)	81 (32%)	26 (36%)	
General Surgery	113 (35%)	85 (34%)	28 (39%)	
Surgical Specialities	105 (32%)	87 (34%)	18 (25%)	
Antimicrobial allergy	75 (23%)	61 (24%)	14 (19%)	0.41
Comorbidities				
Immunosuppression	39 (12%)	34 (13%)	5 (7%)	0.13
Previous MI	33 (10%)	22 (9%)	11 (15%)	0.10
CCF	25 (8%)	20 (8%)	5 (7%)	0.79
PVD	10 (3%)	7 (3%)	3 (4%)	0.54
Cerebrovascular disease	37 (11%)	26 (10%)	11 (15%)	0.24
COPD	54 (17%)	43 (17%)	11 (15%)	0.73
Diabetes	74 (23%)	51 (20%)	23 (32%)	0.04
CKD	37 (11%)	26 (10%)	11 (15%)	0.24
Liver disease	41 (13%)	37 (15%)	4 (6%)	0.04
Malignancy	87 (27%)	64 (25%)	23 (32%)	0.26
Charlson comorbidity score (IQR)	2 (0–4)	2 (0–4)	2 (1–4.25)	0.11
>1 piece of PAF advice	95 (29%)	64 (25%)	31 (43%)	0.003
Justification for advice provided	298 (92%)	232 (92%)	66 (92%)	0.99
Verbal communication (n = 268)[a]	63 (19%)	51 (20%)	12 (28%)	0.54
Outcome				
Length of stay (IQR)	3 (1–7)	3 (1–6)	4 (2–7)	0.14
Duration of inpatient antimicrobials after PAF (IQR)	2 (1–5)	2 (1–4)	3 (1–5)	0.005
Clostridium difficile infection (inpatient)	2 (0%)	2 (1%)	0 (0%)	0.45
Acute kidney injury (inpatient)	10 (3%)	6 (2%)	4 (6%)	0.17
Inpatient mortality	10 (3%)	7 (3%)	3 (4%)	0.54
ICU admission (inpatient)	4 (1%)	3 (1%)	1 (1%)	0.89
Infection related 30-day readmission (Y/N)[b]	21/294 (7%)	15/231 (6%)	6/63 (10%)	0.44

IQR = interquartile range; MI = myocardial infarction; CCF = congestive cardiac failure; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PAF = prospective audit and feedback; ICU = intensive care unit; Y/N = yes/no.

[a] Documentation of verbal communication with clinicians was only available for a subset of patients.

[b] Data missing for ten patients.

Table 2
Summary of findings from multivariate analysis of independent predictors for adherence to prospective audit and feedback advice.

	Odds ratio	95% confidence intervals	P-value
Liver disease	3.31	1.22–11.66	0.03
Diabetes	0.49	0.27–0.91	0.02
>1 piece of PAF advice provided	0.42	0.23–0.73	0.002
Patient receiving piperacillin/tazobactam (vs. other agents)	0.45	0.25–0.80	0.008

PAF = prospective audit and feedback.

(n = 193). Other antimicrobials were prescribed less commonly; this included ceftriaxone (n = 48), meropenem (n = 34), and vancomycin (n = 32).

Adherence to PAF was associated with a significantly shorter median duration of inpatient antimicrobial use following PAF advice (2 versus 3 days, $P = 0.005$; Table 2). There were no differences in *Clostridium difficile* infection, acute kidney injury, intensive care admissions, in hospital length of stay, or mortality of infection related readmissions within 30 days. Of the different antimicrobials, only receipt of piperacillin/tazobactam (n = 193) was significantly associated with non-adherence to PAF advice ($P = 0.02$). On multivariate analysis, an independent predictor for adherence was patients with liver disease (odds ratio [OR] 3.31, 95% confidence intervals [1.22–11.66], $P = 0.03$). Adherence was less likely in patients with diabetes (OR 0.49 [0.27–0.91], $P = 0.02$), when more than one piece of advice was provided (OR 0.42 [0.23–0.73], $P = 0.002$), and when the patient was receiving piperacillin/tazobactam when compared with other antimicrobials (OR 0.45 [0.25–0.80], $P = 0.008$).

We have demonstrated that clinicians were non-adherent to antimicrobial stewardship PAF advice for nearly one quarter of patients. When clinicians adhered to PAF advice, the subsequent duration of inpatient antimicrobial use was reduced by one third without adversely impacting infection-related outcomes including inpatient mortality or infection-related readmission rates.

The rate of non-adherence to PAF in our setting accords with data published elsewhere [3–5] and may reflect clinician's wary attitudes towards unsolicited PAF advice, particularly as it may be perceived by clinicians to delay care and threaten their prescribing autonomy [12]. It may also reflect the inherent limitations of PAF, which does not include bedside assessment for patients with complex conditions, as illustrated by formal ID consultation being recommended for 9% of patients in our study.

A better understanding of risk factors may facilitate efforts to improve adherence of PAF. Our finding of an association between piperacillin/tazobactam use is consistent with previous findings of broad-spectrum therapy as a risk factor for non-adherence [13]. Additionally, we have identified that provision of more than one piece of advice as a novel risk factor for non-adherence to PAF advice. As has been proposed for formal ID consultations, limiting the number of pieces of advice and ensuring that the advice is legible, organized and accompanied by justification may improve adherence to advice [14]. Although not supported by our study, others have shown that surgical specialities are associated with non-adherence to PAF advice [3], as is failure to provide verbal advice alongside written recommendations [4]. The type of advice and the seniority of the clinician receiving the advice have also been shown to influence adherence [5].

Our observation that adherence to PAF advice was associated with a reduced duration of antimicrobial use was not surprising, given that reduced duration or cessation of antimicrobial therapy were the second most frequent type of advice given. The magnitude of benefit we observed is consistent with other's published experience. For example Liew et al. [6] demonstrated a nearly 50% reduction in duration of antimicrobial use in addition to a reduction in 30 day all-cause mortality associated with adherence to PAF advice for empirical therapy. Whilst we observed a trend towards a reduced length of stay in association with adherence to PAF advice, our study may have been under-powered to detect significant differences for other meaningful clinical outcomes.

Despite the use of a standardised definitions and a data collection form, the completeness of our data is limited by retrospective extraction of data from an electronic medical record. The low frequency of important clinical outcomes precluded multivariate analysis with relation to adherence, increasing the risk of confounding. Finally, we did not perform an assessment of cost implications of non-adherence. This requires further study as whilst a reduction in antimicrobial expenditure has been associated with the introduction of a PAF program [15], a specific association between adherence and cost savings has not been made.

In conclusion, failure to adhere to PAF advice is not uncommon and is associated with more prolonged antimicrobial use. By identifying risk factors for non-adherence to PAF advice, AMS services could improve adherence by targeting advice given to patients with particular clinical, antimicrobial, or advice-related characteristics. Importantly, adherence was not associated with inferior infection-related patient outcomes, reassuring clinicians that provision of unsolicited PAF advice is a safe and effective AMS intervention.

Conflicts of interest

None.

Contribution

CH (study design, data collection, manuscript write-up and review), MR (study design, data collection, manuscript write-up and review), LM (study design, statistical analysis, manuscript write-up and review), PI (study concept and design, data collection, manuscript write-up and review).

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