Real-time monitoring of antimicrobial use density to reduce antimicrobial resistance through the promotion of antimicrobial heterogeneity in a haematology/oncology unit

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Background: In haematology/oncology units, the frequent and heavy use of broad-spectrum antimicrobials can lead to outbreaks of antimicrobial resistance. Increasing antimicrobial heterogeneity might be a useful strategy for preventing such resistance.

Methods: A real-time antimicrobial use density (AUD) monitoring system (RAMS) was developed to precisely assess antimicrobial heterogeneity. This study was prospectively conducted over a 39 month period and involved 970 patients. Patient-specific antimicrobial therapy with five carbapenems (meropenem, biapenem, panipenem/betamipron, imipenem/cilastatin and doripenem) and four non-carbapenems (piperacillin/tazobactam, ceftazidime, cefozopran and cefepime) was prescribed in the first 12 months. A first-line antimicrobial was selected from among nine antimicrobials according to a predetermined schedule for the next 15 months. AUD-based antimicrobial selection was implemented using the RAMS during the last 12 months. We compared our findings for the RAMS period with those for the other periods to determine the effects of RAMS-based AUD monitoring on antimicrobial resistance.

Results: The mean absolute difference between the AUD values of carbapenems and non-carbapenems (AUD deviation) was 6.0% in the RAMS period (range 0.5%–15.8%) and antimicrobial heterogeneity (AUD deviation ≥10%) was achieved in 10 out of 12 months (83.3%). Furthermore, during the RAMS period, AUD deviation was significantly smaller and the frequency of outbreaks of antimicrobial-resistant strains other than Stenotrophomonas maltophilia was significantly decreased (from 7.9% to 3.5%; P < 0.01) compared with the other periods.

Conclusions: The longer period of stable antimicrobial heterogeneity achieved by the RAMS strengthened its preventive effects against antimicrobial resistance. Optimal antimicrobial heterogeneity based on real-time AUD monitoring could reduce the frequency of outbreaks of antimicrobial resistance.

Introduction

Bacterial infections remain a major complication in haematology/oncology units and are associated with relatively high mortality rates in immunocompromised patients and patients with chemotherapy-induced neutropenia.1,2 The frequent use of interventions involving the same antimicrobials in units where patients often require constant antimicrobial treatment for long periods can promote antimicrobial resistance related to MRSA, ESBL-producing strains, Pseudomonas aeruginosa and Stenotrophomonas maltophilia.3,4

Possible strategies for preventing nosocomial antimicrobial resistance include reducing the amount of antimicrobials administered or using a wider range of antimicrobials (increasing antimicrobial heterogeneity).5–7 Management strategies aimed at increasing antimicrobial heterogeneity have been implemented through the introduction of antimicrobial mixing or cycling;8–10 however, the benefits of these strategies are uncertain.

Antimicrobial use density (AUD), expressed as DDDS/1000 patient-days, has recently been employed to assess antimicrobial use.4,11 We therefore developed a real-time AUD monitoring system (RAMS) to enable the precise control of antimicrobial heterogeneity, and subsequently confirmed that increasing antimicrobial heterogeneity is a useful strategy against antimicrobial resistance.

Patients and methods

Patients

A total of 970 consecutive adult patients with haematological malignancies such as leukaemia, malignant lymphoma and myeloma participated in this study (Table S1, available as Supplementary data at JAC Online).
Study design

This study was designed as a prospective monocentre observational study. It was conducted over a 39 month period between April 2009 and June 2012 and was approved by the institutional review board at Wakayama Medical University. The study procedures also conformed to the Helsinki Declaration and informed consent was obtained from all patients. Three consecutive time periods were defined and a different antimicrobial selection strategy was used for the empirical treatment of fever in each period. Throughout the study period, antimicrobials were selected from among nine restricted antimicrobials, including five carbapenems (meropenem (1 g, every 8 h), biapenem (0.3 g, every 6 h), panipenem/betamipron (0.5 g, every 6 h), imipenem/cilastatin (0.5 g, every 6 h) and doripenem (0.5 g, every 8 h)) and four non-carbapenems (piperacillin/tazobactam (4.5 g, every 6 h), ceftazidime (1 g, every 6 h), ceftozopran (1 g, every 6 h) and cefepime (1 g, every 6 h)). In the initial 12 months, patient-specific antimicrobial therapies were prescribed at the discretion of the individual doctors. In the subsequent 15 months, a first-line antimicrobial was selected by the principal investigator from among nine antimicrobials according to a predetermined schedule (meropenem → ceftozopran → biapenem → ... → cefepime), in which antimicrobial use was distributed equally among the patients (conventional mixing (CM)).

The AUD-based selection of antimicrobials with the RAMS was implemented in the last 12 months of the study (Figure S1). Antimicrobial treatment was discontinued when the patients became afebrile, were negative for inflammatory indicators and had a neutrophil count of ≥0.5×10⁹/L. Anti-MRSA agents and granulocyte colony-stimulating factors were not prescribed empirically. Protocol deviations were allowed if a history of hypersensitivity to a specific antimicrobial was reported or a pathogen that was not susceptible to the selected antimicrobial was isolated. In such cases, patients were treated with the appropriate antimicrobials.

RAMS

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\text{AUD} = \left( \frac{\text{total antimicrobial use (g)}}{\text{DDDs (days)}} \right) \times 1000 \text{ patient-days}
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To quantify the degree of antimicrobial heterogeneity (i.e. carbapenems versus non-carbapenems), we created a RAMS calculator to determine both the AUD and the difference in AUD (AUD deviation) in real time using Microsoft Excel software (Microsoft, Redmond, WA, USA) (Figure S1). An AUD deviation value of 0% indicates an equal use of specific classes of antimicrobials or individual antimicrobials.

Statistics

Infectious episodes in the same patient were analysed as independent events if they were separated by an interval of 72 h. Continuous variables were analysed using the Mann–Whitney U-test and Fisher’s exact test where appropriate. P values <0.05 were considered significant.

Figure 1. Relationship between the AUD deviation and the frequency of outbreaks of antimicrobial-resistant strains. Changes in AUD deviation between carbapenems and non-carbapenems over time are shown in the line chart. The open and filled circles represent AUD deviations of <10% and ≥10%, respectively. The monthly incidence of antimicrobial-resistant bacteria in the four classes of MRSA, S. maltophilia, P. aeruginosa and ESBL-producing E. coli are shown in the bar chart.
Results

AUD monitoring helped to prevent antimicrobial resistance

The mean absolute AUD deviation between carbapenems and non-carbapenems was 6.0% (range 0.5%–15.8%) in the RAMS period, 12.6% (range 0.1%–31.7%) in the CM period without AUD monitoring and 11.4% (range 1.1%–33.2%) in the non-interventional control period (Figure 1). The target design of antimicrobial heterogeneity (AUD deviation <10%) was accomplished in 10 out of 12 months during the RAMS period (83.3%) and was maintained for significantly longer during the RAMS period than in the CM or control periods, in which antimicrobial heterogeneity was only achieved in 7 of 15 months (46.7%) and 6 of 12 months (50.0%), respectively (P<0.05). We then investigated the incidence rates of antimicrobial-resistant bacteria in three classes, i.e. MRSA, S. maltophilia and others (e.g. P. aeruginosa and ESBL-producing Escherichia coli), in each period (Figure 1). The crude incidence data showed that there were 21 antimicrobial resistance events (7.4%) in the RAMS period, whereas 41 antimicrobial resistance events (11.0%) occurred during the CM period and 37 antimicrobial resistance events (11.8%) were seen during the control period (Figure 2). The frequency of outbreaks of antimicrobial-resistant strains other than S. maltophilia was significantly reduced in the RAMS period (from 7.9% to 3.5%; P<0.01) (Figure 2). There were no significant differences in the incidence of febrile episodes among the three periods (data not shown).

Effects of AUD monitoring on the prevention of MRSA and S. maltophilia infections

We analysed the effect of the length of time over which the AUD deviation value was <10% on the frequency of S. maltophilia isolates (Figure S2). The figure shows several interesting points: (i) the number of consecutive months in which antimicrobial heterogeneity was achieved was negatively correlated with the frequency of S. maltophilia outbreaks; (ii) S. maltophilia was commonly detected in the month following the first month in which the AUD deviation exceeded 10%; and (iii) a prolonged period of antimicrobial heterogeneity suppressed the outbreak of antimicrobial resistance after the value for AUD deviation rose to ≥10%. As with S. maltophilia, MRSA outbreaks gradually became less common during periods of sustained antimicrobial heterogeneity (Figure S2).

Discussion

We demonstrated here that real-time AUD monitoring with our RAMS (Figure S1) allowed us to ensure that carbapenems and non-carbapenems were used at similar frequencies. The frequency of outbreaks of antimicrobial resistance within our haematology/oncology unit was simultaneously reduced (Figure 1). This is the first study to assess the effects of antimicrobial mixing in a haematology unit. Conversely, an AUD-monitoring-independent approach that aimed to increase antimicrobial heterogeneity, i.e. the CM protocol, led to an imbalance in the frequencies of carbapenem and non-carbapenem use (Figure 1) and did not reduce the frequency of antimicrobial resistance (Figure 1). The interventions used in the present study did not result in any significant change in the total consumption of antimicrobials or carbapenems (Table S1). These results suggested that the weak effects of the interventions reported in previous studies might have been partly due to a lack of antimicrobial heterogeneity. In addition, it was found that, over time, other methods that aimed to promote antimicrobial heterogeneity, such as the introduction of a cycling strategy, had little beneficial impact on the inhibition of Gram-positive bacteraemia. Thus, it is conceivable that AUD monitoring and a real-time mixing approach might resolve the issues affecting antimicrobial heterogeneity strategies and help to prevent the development of resistance to a wide range of antimicrobials.

Our RAMS elicited beneficial effects regardless of the patients’ profiles, including their age, their gender and the type of haematological disorder that they had (Table S1). Moreover, the longer period of sustained antimicrobial heterogeneity achieved by the RAMS strengthened its preventive effects against several antimicrobial-resistant species such as MRSA and S. maltophilia, which have different characteristics (Figure S2).

Figure 2. Incidence rate of all antimicrobial-resistant bacteria (top panels) or antimicrobial-resistant bacteria other than S. maltophilia (bottom panels) in each period (left-hand panels) or in the with-AUD (RAMS period) and without-AUD [AUD (–)] monitoring periods (right-hand panels).
Thus, much larger studies are required to draw firm conclusions regarding the utility of AUD monitoring for preventing antimicrobial resistance.

This study suggested that the controlled promotion of antimicrobial heterogeneity, without reducing the total amount of antimicrobials administered, played a role in controlling antimicrobial resistance in our unit. It would be interesting to evaluate the efficacy of AUD monitoring using our RAMS for other classes of carbapenems, penicillins and cephalosporins. Our RAMS could be a useful way of achieving a consistent and sustainable degree of antimicrobial heterogeneity in clinical practice, which could lead to a lower rate of complications related to antimicrobial-resistant infections. Therefore, the utility of our RAMS in patients with other disorders and in other institutes merits further research.

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Transparency declarations
None to declare.

Author contributions
S. M. and N. H. designed the study, performed the research, analysed the data and wrote the manuscript. T. M., K. K., H. H., M. K., J. W., A. N. and T. S. analysed the patients' clinical data. H. N. supervised the project.

Supplementary data
Table S1, Figure S1 and Figure S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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