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Effect of systemic antibiotics and topical chlorhexidine on meticillin-resistant *Staphylococcus aureus* carriage in intensive care unit patients

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SUMMARY

Antibiotics and antiseptics have the potential to influence carriage and transmission of meticillin-resistant *Staphylococcus aureus* (MRSA), although effects are likely to be complex, particularly in a setting where multiple agents are used. Here admission and weekly MRSA screens and daily antibiotic and antiseptic prescribing data from 544 MRSA carriers on an intensive care unit (ICU) are used to determine the effect of these agents on short-term within-host MRSA carriage dynamics. Longitudinal data were analysed using Markov models allowing patients to move between two states: MRSA positive (detectable MRSA carriage) and MRSA negative (no detectable carriage). The effect of concurrent systemic antibiotic and topical chlorhexidine (CHX) on movement between these states was assessed. CHX targeted to MRSA screen carriage sites increased transition from culture positive to negative and there was also weaker evidence that it decreased subsequent transition from negative back to positive. In contrast, there was only weak and inconsistent evidence that any antibiotic influenced transition in either direction. For example, whereas univariate analysis found quinolones to be strongly associated with both increased risk of losing and then reacquiring MRSA carriage over time intervals of one day, no effect was seen with weekly models. Similar studies are required to determine the generalisability of these findings.

Introduction

Several studies have reported an association between antibiotic consumption and acquisition or transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) via both patient-level and group-level effects.[1,2] This might reflect different mechanisms: antibiotics inactive against MRSA might increase carriage by exposing a niche previously occupied by endogenous bacteria (including meticillin-susceptible *S. aureus*), whereas antibiotics active against MRSA might reduce carriage by killing MRSA.[3] The outcome of these divergent effects is difficult to predict, particularly when multiple concurrent antibiotics are used.

Here we focus on the effect of systemic antibiotics and topical chlorhexidine (CHX) on short-term within-host colonisation dynamics, excluding the important but complex effect of antibiotics on person-to-person transmission. Although some studies have considered risk factors associated with persistence of MRSA carriage, the short-term effect of different antibiotics on within-host colonisation appears only to have been investigated for antimicrobials that deliberately target staphylococcal carriage.[2,4–6]

To our knowledge there have been no previous attempts to study systematically the effects of all antibiotics and antiseptics on MRSA carriage among colonised patients on an intensive care unit (ICU). This is important because reduced colonisation is associated with reduced transmission, and MRSA colonisation is an important risk factor for developing MRSA infection.[7] Surface decolonisation is increasingly used to reduce infection rates, particularly those associated with vascular catheters.[8–11] This study uses a longitudinal modelling approach to analyse individual-level MRSA

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screening results and daily antimicrobial use data to evaluate the effect of antimicrobials on MRSA carriage.

Methods

Study setting and data collection

Clinical setting and practice

All patients admitted to two 15-bed general ICUs between 1 January 2002 and 20 April 2006 from whom MRSA was isolated at one or more carriage sites (anterior nares, axillae, groin), and who had one or more subsequent MRSA screens taken, were included in this study. Admission and discharge dates, MRSA screen culture results and daily receipt of systemic antimicrobials or a surface CHX antiseptic protocol were extracted from the Guy's and St Thomas' Staphylococcal Transmission and Antimicrobial Record (G-STAR) database.[12] MRSA screens were taken on day of admission and every Monday morning. A surface CHX antiseptic protocol was commenced on 26 April 2004: MRSA-colonised patients had 1% (w/v) CHX gluconate (Hibitane, Derma, Stotfold, Bedfordshire, UK) applied to nostrils, around the mouth and tracheostomy sites four times daily, 1% CHX acetate powder (CX Antiseptic Dusting Powder, Adams Healthcare, Leeds, UK) applied to groins, axillae and skinfolds daily and were washed daily with 4% CHX (Hibiscrub, SSL International, UK) applied by wet cloth.

Laboratory techniques

MRSA was identified from pooled screening swabs using mannitol salt agar plates (Baird Parker) until July 2004 when a selective mannitol broth method was introduced.[13,14] Isolates were confirmed to be MRSA by tube coagulase and disc diffusion testing methods using meticillin discs.

Modelling assumptions

The sequence of MRSA screening swab collection dates, and dates of starting and stopping all antibiotics and the CHX protocol were included from the date of the first positive MRSA screen.

Models

Discrete-time Markov models were developed to assess the affect of antibiotic and antiseptic treatment on carriage status over time. It is assumed that at each time step, each patient can have one of two possible carriage levels: '+', denoting detectable MRSA carriage, or '−', denoting no detectable MRSA carriage.

Model 1 (daily transitions)

Model 1 considers the effect of a single antimicrobial treatment, i.e. a given single type of antibiotic or antiseptic agent. It is known whether or not each patient was receiving the specified antimicrobial each day. We assume that a patient who is '+' and receiving the antimicrobial on a given day has probability p_a of becoming '−' on the next day, i.e.

$$P(\text{patient is '}-\text{' at time step } j+1, \text{ given that patient is '}+\text{' and receiving antimicrobial at time step } j) = p_a,$$

whereas if the patient is not receiving the antimicrobial on day j then this probability is p_n. We similarly define

$$P(\text{patient is '}+\text{' at time step } j+1, \text{ given that patient is '}-\text{' and receiving antimicrobial at time step } j) = q_a,$$

with q_n the corresponding probability if the patient is not receiving the antimicrobial on day j.

The model has four parameters: p_a, q_a, p_n and q_n. The effect of the antimicrobial on daily transition probabilities can be expressed via the odds ratios $p_a(1-p_n)/p_n(1-p_a)$ and $q_a(1-q_n)/q_n(1-q_a)$. Odds ratios >1 indicate that the antimicrobial is associated with an increased probability of a transition from detectable carriage to undetectable carriage in the first case, and an increased probability of a transition from undetectable to detectable carriage in the second. Standard methods can be used to derive estimates and confidence intervals for the model parameters and odds ratios.

Models 2.1 and 2.2 (weekly transitions)

Further simplifications were made by changing the time step to one week, and using data only from tests that took place at weekly intervals. Since the vast majority of tests were of this kind, this approach retains most data points, but is computationally simpler. Nevertheless, for each patient there are daily data on antibiotic and antiseptic usage and so simplifying assumptions are needed for a weekly model. For model 2.1, patients were considered to be receiving the antimicrobial in a given week if, and only if, they received it for at least four days in that week. The effect of this assumption was assessed by performing sensitivity analyses in which this four-day threshold was changed to three or five days.

Transition probabilities were defined using a logistic regression approach (model 2.1):

$$\log\left(p_{ij}/\left(1-p_{ij}\right)\right) = a + b^{*}x_{ij} \quad (1a)$$

$$\log\left(q_{ij}/\left(1-q_{ij}\right)\right) = c + d^{*}x_{ij} \quad (1b)$$

where p_{ij} and q_{ij} denote the respective probabilities of '+' to '−' and '−' to '+' for patient i in week j and x_{ij} takes the value 1 if patient i is considered to be receiving the antimicrobial in question in week j and is zero otherwise. The parameters a, b, c, d are constants to be estimated, while $\exp(b)$ and $\exp(d)$ give the odds ratios for the effect of the antimicrobial on '+' to '−' and '−' to '+' transitions respectively.

We also consider another approach (model 2.2) where x_{ij} represents the number of days that patient i receives the antimicrobial in week j. Here, the odds ratios $\exp(b)$ and $\exp(d)$ represent the effect of each additional day of treatment on the carriage state transition probabilities.

Model 3 (weekly transitions, multivariate model)

Instead of considering one drug at a time, the effect of multiple antimicrobial use each week was described using a multiple logistic regression model and analysed using a Bayesian model averaging (BMA) approach.[15] This approach accounts for individual model uncertainty and the odds ratios obtained for each antimicrobial are weighted averages of those obtained from the most plausible models.

Results

In all, 544 out of 4570 ICU admissions had more than one subsequent MRSA screen taken following an initial positive screen and were included in the analysis. These patients had 1268 MRSA screens taken during a period of 10,066 ICU days of which 909 screens were culture positive and 359 were culture negative. One or more antibiotics were prescribed on 7301 of the 10,066 days. The number of treatment days with each antimicrobial class was: bisbiguanides (CHX) 3694; glycopeptides 2898; nitroimidazoles 1133; macrolides 1278; cephalosporins 1312; aminoglycosides 1118; quinolones 549; penicillins 639; polymixins 161; rifamycins 128; oxazolidinones 118.