Risk factors for carbapenemase producing (CP) carbapenem resistant enterobacteriaceae (CRE) versus non-carbapenemase producing (non-CP) CRE: An analysis of the Carbapenemase Producing Enterobacteriaceae in Singapore (CaPES) cohort

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Background: Singapore is currently in the fourth year of a CP CRE epidemic. Carbapenem resistance primarily occurs through the acquisition of carbapenemase genes or through a combination of extended-spectrum beta-lactamase- or ampC-production and porin loss. Antibiotic pressure and horizontal transmission are important in the successful spread of CRE. This study was conducted to identify clinical risk factors for CP CRE compared to non-CP CRE in Singapore. **Methodology**: Since December 2013, prospective clinical and microbiological data obtained from patient interviews and electronic health records, are being collected for consenting patients with clinical or surveillance CRE isolates from six public hospitals in Singapore, as part of the CaPES study. Here, we described the cohort and identified risk factors for CP CRE patients by comparing it with non-CP CRE. **Results**: Between (date) December 2013 and 31 July 2014, 106 of 282 patients with CRE isolates were recruited into the study. Data from 78 patients (52 CP CRE and 26 non-CP CRE) with complete data was analysed. There were no significant differences in age, sex, ethnicity and Charlson comorbidity index between CP CRE and non-CP CRE patients (Table 1). More CP CRE were isolated from surveillance swabs (66.5% vs 30.8%, P=0.004). Among the CP CRE patients, 42.3%, 44.2% and 17.3% were carrying bla_{NDM}, bla_{KPC}, and $bla_{\text{OXA-48-like}}$ carbapenemases respectively. Clinical infections were more likely in the non-CP CRE group (46.2% vs 23.1%, P=0.04). Significantly more CP CRE patients had travel history during the preceding 1 year (44.2% vs 19.2%, P=0.03) but fewer had exposure to carbapenems (17.3% vs 38.5%, P=0.04) compared to non-CP CRE. South Asia and East Asia were common travel destinations for CP CRE compared to non-CPCRE patients. However, contact with overseas healthcare providers was not identified as a risk factor for CP CRE (9.6% vs 3.9%, P=0.37). On multivariate analysis, travel history was the only independent risk factor for CP CRE (OR 5.79; 95% CI, 1.32-25.31; P=0.02) in Singapore. **Conclusions**: Four years into the epidemic, travel history remains a significant risk factor for CP CRE. Active surveillance of patients with overseas travel, especially to South and East Asia, should be considered.

Table 1. Univariate and multivariate analysis of CPCRE compared to non-CPCRE

Variables	CP CRE (n=52) (%)	Non-CP CRE (n=26) (%)	P[#]	Multivariate analysis OR (95% CI)	P
Age, median years (IQR)	65 (57.5 - 70.5)	63 (52 - 73)	0.53*		
Sex, male	32 (61.5)	19 (73.1)	0.31		
Ethnicity			0.44		
Chinese	37 (71.2)	16 (61.5)			
Malay	5 (9.6)	6 (23.1)			
Indian	4 (7.7)	2 (7.7)			
Others	6 (11.5)	2 (7.7)			
Specimen type[##]					
Rectal swab	34 (65.4)	8 (30.8)	0.004		
Bile	1 (1.92)	4 (15.4)	0.04		
Urine	7 (13.5)	8 (30.8)	0.07		
Blood	3 (5.8)	3 (11.5)	0.40		
Wound swab	6 (11.5)	2 (7.7)	0.71		
Others	7 (13.5)	3 (11.5)	>0.99		
Organisms			0.63		
Klebsiella pneumonia	23 (44.2)	12 (46.2)			
Escherichia coli	11 (21.2)	7 (26.9)			
Enterobacter spp.	9 (17.3)	6 (23.1)			
Klebsiella spp.	6 (11.5)	1 (3.9)			
Others	3 (5.8)	0			
Clinical infection[##]	12 (23.1)	12 (46.2)	0.04		
Charlson score > 2	43 (82.7)	18 (69.2)	0.18	3.10 (0.56 - 17.17)	0.2
Travelled for more than 3 days in last 1 years**	23 (44.2)	5 (19.2)	0.03	5.79 (1.32 - 25.31)	0.02
South Asia	5 (9.6)	0	0.16		
East Asia	8 (15.4)	0	0.05		
South East Asia	4 (15.4)	10 (19.2)	0.76		
Others	2 (3.9)	0	0.55		
Overseas healthcare contact	5 (9.6)	1 (3.9)	0.37		
Hospitalised in the previous year	37 (71.2)	14 (53.9)	0.13	1.70 (0.53 - 5.46)	0.37
Invasive procedures in the previous year	36 (59.2)	14 (53.9)	0.18	1.45 (0.39 - 5.43)	0.58
MDRO in the previous year	21 (40.4)	6 (23.1)	0.13	1.93 (0.54 - 6.97)	0.31
Exposed to antibiotics in the previous 30 days	41 (78.9)	22 (84.6)	0.54		
Carbapenems	9 (17.3)	10 (38.5)	0.04	0.33 (0.10 - 1.10)	0.08
Fluoroquinolones	10 (19.2)	1 (3.9)	0.07	6.01 (0.60 - 59.89)	0.13
Extended spectrum penicillin	29 (55.8)	14 (53.9)	0.87		
ICU admission before CRE	13 (25.0)	3 (11.5)	0.17		
Indwelling devices	30 (57.7)	16 (61.5)	0.75		
Time at risk, median day (IQR)	4 (11 - 27)	3 (13 - 30)	0.89*		
LOS, median days (IQR)	18 (36.5 - 53)	18 (29 - 67)	0.75*		

*Rank sum test

[#]Pearson Chi Square

**More than one region may be travelled by a subjects

[##]Not included in multivariable model

MDRO, multidrug resistant organisms; ICU, intensive care unit; LOS, length of stay

Transmission Tracking of Methicillin Resistant *Staphylococcus aureus*(MRSA) in the Intensive Care Unit, UKM Medical Centre (UKMMC) Via Molecular Characterizationand Geographic Information System (GIS) analysis

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Background: Methicillin-Resistant*Staphylococcus aureus* (MRSA) is an important pathogen associated with hospital infection. In this study, we tracked the transmission of MRSA in the Intensive Care Unit (ICU) of our hospital via molecular characterization and Geographic Information System (GIS) analysis of strains isolated from affected patients, their surrounding environment and attending health care workers.

Methods: The study was conducted in a 24-bed ICU of UKM Medical Centre (UKMMC), from February 2013 to February 2014. MRSA isolates from ICU patients hospitalized during the period were retrieved and purified as strains. The surrounding environmentof MRSA-positive patients (bed linen, ventilator, bed side rail and flooring) and their attending health care workers were also swabbed to detect MRSA. Isolates were confirmed to be MRSA viaCefoxitinMannitol Salt Agar screening, coagulase test and *mecA*PCR amplification. SCC*mec* and multiple-loci VNTR analysis (MLVA) genotyping were performed for all strains. GIS was employed to identify MRSA transmission in the ICU, whereby assessment of MRSA strain relatedness and integration of bacterial molecular and patient spatial data enabled identification of MRSA transmission.

Results: Sixteen MRSA was isolated from the ICU during the study duration, where 11 strains were from patients, while 5 strains were isolated from the environment of3 patients (patients #2, # 5 and #8). MRSA were obtained from the bed side rails of patient #2, bed linen, ventilator and flooring of patient #5, and flooring of patient #8. Interestingly, no MRSA was isolated from the attending health care workers. FourMRSA clones (designated as α, β, γ and δ) were found to be circulating in the ICU, where11 and 5 strains of the clones were of SCC*mec* types III and V, while 7 and 9 were of MLVA types MLa and MLb, respectively. GIS analysis revealedpositive MRSA patient-environment transmission events in patients #2 and #5 (clones αand β, respectively). We also noted that during the study period, MRSA infections occurred at 6 of the 24 beds (beds #2, #12, #13, #14, #16 and #20), wherebed #16 recorded the most cases (3 cases). Nevertheless, not all clones from these 3 cases were similar (1 clone α, 2 clone β**s).**

Conclusion: Two MRSA patient-environment transmission events were identified in this study. Molecular characterization and GIS analyses proved useful in MRSA transmission tracking.

Preoperative statins use is associated with a lower risk of surgical site infection after coronary artery bypass grafting: A population based cohort study.

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Background: Infectious complications of cardiac surgery are often severe and life threatening. Statins having both immunomodulatory and anti-inflammatory effects are thought to influence the development of postsurgical infections. We examined the association between statin use and risk of surgical site infections in patients undergoing cardiac surgery.

Methods: A population-based cohort of patients who underwent coronary artery bypass graft surgery (CABG) study was conducted to describe the epidemiologic features of surgical site infections (SSI) or leg harvest site infections (LHSIs) in Olmsted County, Minnesota, USA, between January 1, 1993, and December 31, 2008. Logistic regression analysis was used to examine the association between preoperative statins use and post CABG SSIs LHSIs. The effect of preoperative statins use was further adjusted for statins doses and classes (Hydrophilic and Lipophilic) in separate models. All the statistical analyses were performed using Stata (version 12; StataCorp LLP).

Results: 1421 residents of Olmsted County underwent CABG surgery. The overall SSI incidence rate was 7.0% (95% CI, 5.7%-8.4%). The incidence rate of superficial sternal SSI was 2.0% (95% CI, 1.2%-2.7%) and of deep sternal SSI was 1.5% (95% CI, 0.9%-2.2%). The LHSI rate was 3.6% (95% CI, 2.6 %-4.5%). Preoperative statins therapy was associated with a reduced odds of postoperative infections among patients with adjusted OR was 0.26 (95% CI, 0.08 to 0.86; p=0.028). When the statins classes and doses effect were assessed, adjusted ORs for lipophilic statins were: moderate dose 0.45 (95% CI, 0.27 to 0.76) and for high dose 0.26 (95% CI, 0.08 to 0.86) (Table)

Table:

Variables	Adjusted OR (95% CI)	OR adjusted for statins doses (95% CI)
Statins classes		
Hydrophilic	0.59 (0.17, 1.97)	0.30 (0.05, 1.69)
Lipophilic*	0.45 (0.28, 0.70)	0.26 (0.08, 0.86)
Body mass index **(**BMI ≥30)*	2.37 (1.53, 3.67)	2.40 (1.54, 3.72)
Insulin dependent*	2.26 (1.34, 3.81)	2.26 (1.34, 3.80)
Immunosuppressive Treatment*	2.71 (1.20, 6.13)	2.64 (1.16, 5.98)
Number of internal mammary arteries grafts (1-2)*	0.40 (0.22, 0.74)	0.41 (0.22, 0.75)
Post-Operative plasma transfusion*	2.00 (1.18, 3.37)	2.04 (1.21, 3.44)
Number of Diseased Coronary Vessel (≥2)*	3.72 (1.13, 12.20)	3.66 (1.12, 12.02)

* Statistically significant at $p<0.05$.

Conclusion: In this population-based study of patients undergoing CABG surgery, we found a dose dependent and class specific association between statins use and lower risk of postoperative surgical infections. This important association needs to be further examined in randomized trials.

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Investigation of external factors on the development of surgical site infections (SSI)

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Background:

Surgical site infection(SSI) is a serious complication leading to increased mortality and length of hospital stay, a 5-fold probability of re-hospitalization and excess costs of at least ~ 5000 US-$ per case. It is estimated that up to 30% of SSI is preventable by improvements in the necessary infection control measures. In the "WHO Surgical Safety Checklist" the only item addressing this is the question if antibiotic prophylaxis is given.

Methods:

A retrospective analysis of 156 patients with total hip joint replacement (TEP) was performed to detect risk factors for the development of SSI. Further, 5 TEP operations were monitored concerning adherence of medical personnel to infection control measures by using a standardized checklist. Environmental factors such as microbiological quality of the air during the surgical procedure were followed using sedimentation agar plates and by taking swabs from defined areas in the operating room.

Results:

A high body mass index (BMI) , administration of red blood cells and an ASA score of 4 and higher were significantly associated with the development of SSI. Perioperative prophylaxis was in only 25% of operations applied correctly, in 69% of cases the timing was inadequate; however, an influence on the infection rate was not noticed. The observation of 5 TEP operations revealed that medical personnel not directly involved in the surgical procedure did not adhere to standard infection control measures (non-compliance with personal and hand hygiene). Microbiological quality of the air in the operating theatre did not have a significant effect on infection rates.

Conclusions:

Based on the observations of the surgical procedures, especially the behavior of personnel was regarded as a possible influence factor for the development of SSI. It is suggested to include the following points in a "surgical safety checklist":

- Define perioperative prophylaxis for the period 30-60 min before surgery starts
- Personnel not directly belonging to surgical team adheres to hand and personal hygiene
- Surgical personnel wears double pair of gloves
- Use of a patient warming device

"I wish to be considered for the Young Investigator Award"

The Pharmacodynamics Optimization of Intermittent Vancomycin Dosage Regimens in Methicillin-Resistant *Staphylococcus aureus* Infections with MIC of 1.5 and 2.0 mg/L in Thai Population

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Keywords: Vancomycin, Methicillin-Resistant *Staphylococcus aureus*, Pharmacodynamics

Background
There are increasing number of articles questioning the efficacy of vancomycin to treat methicillin-resistant *Staphylococcus aureus* (MRSA) with MIC 1.5mg/L and 2.0mg/L. However, vancomycin is still used as the cornerstone treatment of MRSA infection particularly in most of developing countries with limited alternative MRSA coverage antibiotics. Owing to the interest whether vancomycin still enable to be used as the cornerstone treatment for MIC 1.5mg/L and 2mg/L, present study was conducted to analyze the achievement of vancomycin desired PK-PD indices in MRSA-infected Thai population.
Methods
Monte Carlo simulation by using 10,000 replications was performed for several vancomycin intermittent dosage regimens ranging from 1g every 6, 8, 12h, 1.5g and 2 g every 12h. Vancomycin concentrations were estimated from population PK study conducted in 212 Thai population. The probability of target attainment (PTA) of each intermittent dosage regimen was calculated from the number of simulated patients who achieved AUC_{24}/MIC $\geq$400 for MIC 1.5mg/L and 2.0mg/L divided by total number of replication.
Results
Dosage regimen 1g every 12h couldn't afford desired PTA for MRSA with MIC 1.5mg/L and 2.0mg/L. Considering the MRSA with MIC 1.5mg/L, dosage regimen 1g every 8h and 1.5g every 12h could afford PTA >80%. However, if particular conditions required PTA >90%, dosage regimen 1g every 6 hours or 2g every 12h should be recommended as the most appropriate dosage regimen. While, for MRSA with MIC 2.0mg/L, only dosage regimens 4g/day, either given as 1g every 6h or 2g every 12h, could afford PTA >80%. No any dosage regimens could afford PTA >90% for MRSA with MIC 2.0mg/L. All PTA achievement represented the PTA at steady state condition.
Conclusions
Intermittent dosage regimen at least 3g/day and 4g/day were needed to afford desired PTA achievement for MRSA with MIC 1.5mg/L and 2.0mg/L, respectively. Finding of present study could be used as a guidance in determining the best intermittent dosage regimen in documented vancomycin treatment. Further study was needed to determine the most appropriate intermittent dosage regimen that could achieve the desired PTA for the 1st 24h.

Immunization with *Staphylococcus aureus* ghost vaccine protected rats from virulent challenge

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Staphylococcus aureus,a Gram-positive bacterium,is one of the important bacterial pathogen which causes a wide range of infections in human and animals. Bacterial ghosts (BGs) are empty bacterial cell envelopes and well-represented as a novel vaccine candidates. In this study, we examined the immunogenicity and protective efficacy of *S. aureus* ghosts (SAGs) against virulent challenge in rats. The non-living SAGs were generated by using the MIC of sodium hydroxide (NaOH). The transmembrane lysis tunnel structure in SAGs was visualized by scanning electron microscopy (SEM). To investigate the SAGs as a vaccine candidate, rats were divided into four groups: group A (non-immunized control), group B (orally immunized), group C (subcutaneously immunized) and group D (intravenously immunized). The specific IgG antibody response of SAG vaccine was significantly increased in immunized groups as compared to non-immunized control group ($P< 0.05$). Moreover, significant increase in population of $CD4^+$ and $CD8^+$ T-cells were observed in all three immunized groups ($P< 0.05$). We also found that the serum bactericidal antibodies were significantly elicited in immunized groups compared to the non-immunized control group ($P< 0.05$). Most importantly, bacterial loads in immunized groups were significantly lower than non-immunized control group ($P< 0.01$). These results suggest that immunization with SAGs induces immune response and provides protection against virulent *S. aureus* challenge.

*Young Investigator Award (I wish to be considered for the Young Investigator Award.)