National Centre for Infectious Diseases

# CONTROL OF CARBAPENEMASE-PRODUCING ENTEROBACTERIACEA IN AN ENDEMIC SETTING:

## DO CLASSICAL IPC METHODS WORK FOR NEW AGE BUGS?

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**Hosted by Jane Barnett**
**jane@webbertraining.com**



## Content

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## Singapore is endemic for major CPEs

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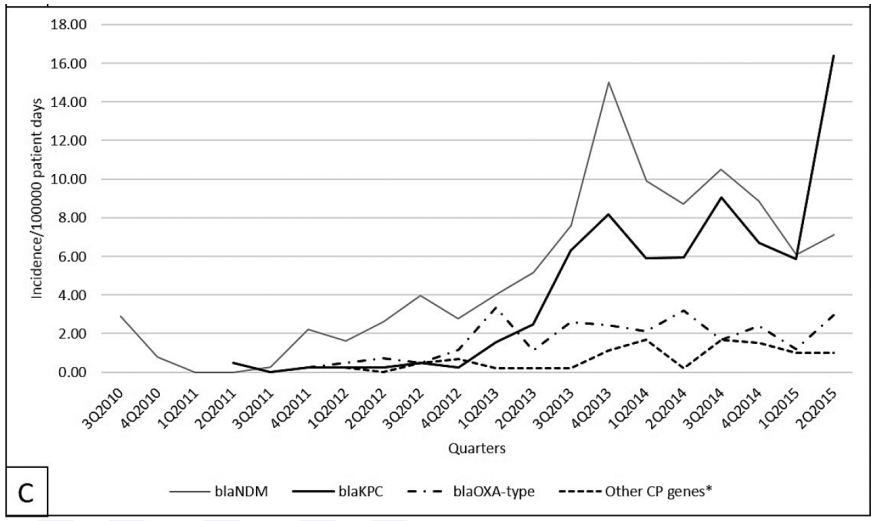


Kalisvar et al; **CID 2017:64 (Suppl 2)**

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## Mechanisms of carbapenem resistance in Enterobacteriaceae

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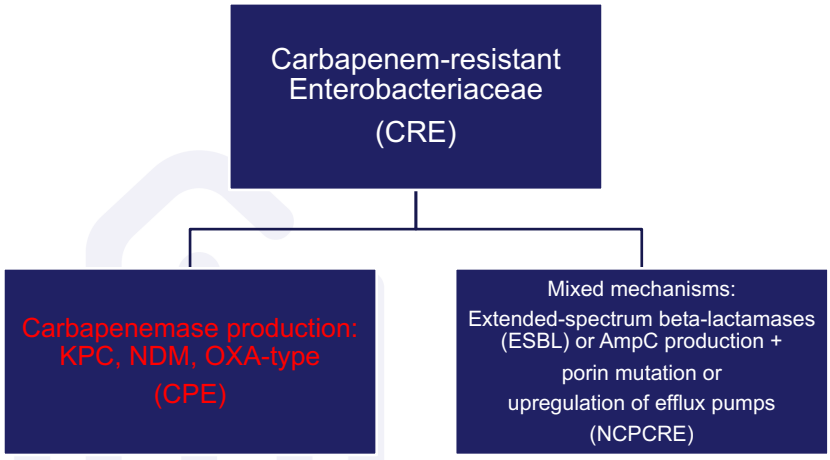


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## Mechanism of resistance and epidemic potential

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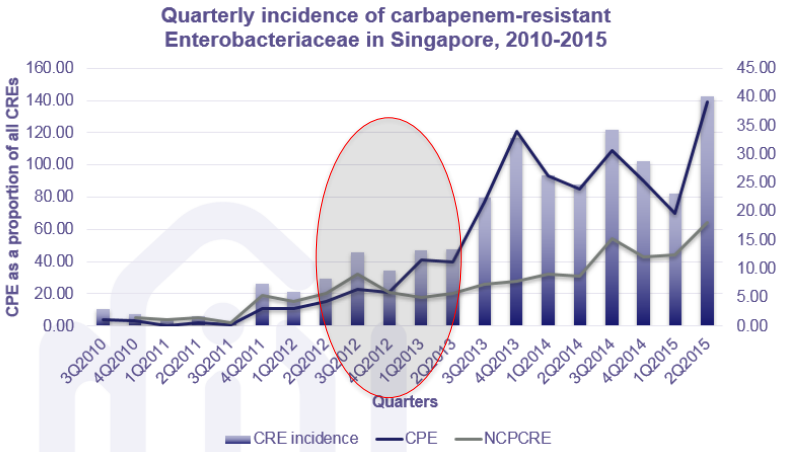


- Since the introduction, CPE had easily taken over NCPCRE

Kalisvar et al; **CID 2017:64 (Suppl 2)**

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## Mechanism of resistance and epidemic potential

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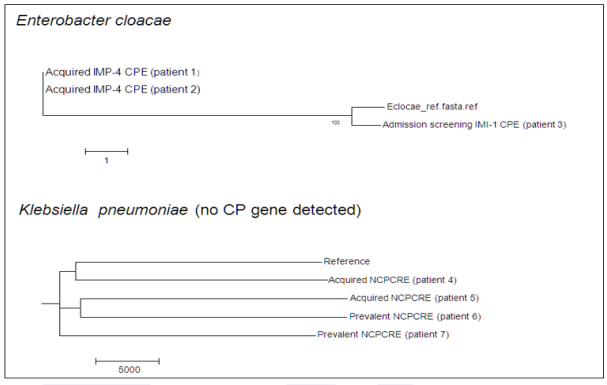


In a prospective ICU screening study, none of the ICU acquired NCPCREs were clonally related.
Two IMP-4 CPEs acquired in ICU were clonally related.

Chia, P.Y. et al. Manuscript under review

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## Mechanisms of resistance and risk factors

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**Table 1. Baseline Characteristics of 249 Hospitalized Patients With Carbapenem-Resistant Enterobacteriaceae (CRE) and Comparative Analysis of Factors Associated With Carbapenemase-Producing Enterobacteriaceae (CPE) and Non–Carbapenemase-Producing CRE (NCPE)**

| | | | | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|---|
| Variables | CRE n = 249 (%) | CPE n = 161 (%) | NCPE n = 88 (%) | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Cerebrovascular disease | 37 (14.9) | 28 (17.4) | 9 (10.2) | 0.13 (0.25–1.21) | .13 | 0.62 (0.26–1.49) | .29 |
| Dementia | 9 (3.6) | 6 (3.7) | 3 (3.4) | 0.91 (0.22–3.74) | >.99 | | |
| Chronic pulmonary disease | 35 (14.1) | 27 (16.8) | 8 (9.1) | 0.50 (0.22–1.15) | .10 | 0.35 (0.14–0.92) | .03 |
| Chronic liver disease | 39 (15.7) | 28 (17.4) | 11 (12.5) | 0.68 (0.32–1.44) | .31 | | |
| Diabetes mellitus | 112 (45.0) | 80 (49.7) | 32 (36.4) | 0.58 (0.34–0.99) | .04 | 0.59 (0.33–1.07) | .08 |
| Chronic kidney disease | 63 (25.3) | 45 (28.0) | 18 (20.5) | 0.66 (0.36–1.23) | .20 | | |
| Solid tumor | 68 (27.3) | 43 (26.7) | 25 (28.4) | 1.09 (0.61–1.95) | .77 | | |
| Hematological malignancies | 25 (10.0) | 10 (6.2) | 15 (17.1) | 3.10 (1.33–7.24) | .01 | 2.85 (1.10–7.41) | .03 |
| Antibiotic exposure in the preceding 30 days | | | | | | | |
| Any antibiotics | 196 (78.7) | 120 (74.5) | 76 (86.4) | 2.16 (1.07– 4.39) | .03 | 1.09 (0.48 – 2.48) | .83 |
| Carbapenems | 84 (33.7) | 38 (23.6) | 46 (52.3) | 3.55 (2.04– 6.17) | <.001 | 3.23 (1.67– 6.25) | <.001 |
| Extended spectrum cephalosporins | 81 (32.5) | 49 (30.4) | 32 (36.4) | 1.31 (0.75 – 2.26) | .34 | | |
| Extended spectrum penicillins | 134 (53.8) | 84 (52.2) | 50 (56.8) | 1.21 (0.71– 2.03) | .48 | | |
| Fluoroquinolones | 47 (18.9) | 25 (15.5) | 22 (25.0) | 1.81 (0.95– 3.45) | .07 | 1.28 (0.61– 2.66) | .51 |
| Aminoglycosides | 28 (11.2) | 14 (8.7) | 14 (15.9) | 1.99 (0.90 – 4.38) | .09 | 1.06 (0.43– 2.65) | .89 |
| Outcomes | | | | | | | |
| Length of hospitalization, median days (IQR) | 38 (17– 65) | 34 (17– 64) | 44 (18 – 66.5) | | .44 | | |

CID 2017:64 (Suppl 2) • Kalisvar et al

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## Mechanisms of resistance and risk factors

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**Table 4** Multivariate analysis of risk factors for *K. pneumoniae* acquisition

| | Porin-ER-*Kp* vs. controls, OR (95 % CI) | *p*-value | KPC-CR-*Kp* vs. controls OR (95 % CI) | *p*-value |
|---|---|---|---|---|
| Acute renal failure | 7.17 (1.33–38.6) | 0.022 | – | – |
| Endoscopy | 6.12 (1.46–25.6) | 0.013 | 6.71 (1.25–36.00) | 0.026 |
| Second-generation cephalosporins | 25.7 (3.20–206.8) | 0.0023 | – | – |
| Third-generation cephalosporins | 2.24 (0.80–6.31) | 0.017 | – | – |
| Carbapenems | 19.10 (4.34–83.9) | <0.001 | 7.74 (1.70–35.02) | 0.008 |

Authors' discussion:

*The main finding of our study was that, when considering independent risk factors, Porin-ER-Kp isolation,more than KPC-CR-Kp, was associated with the number of prior antibiotics, specifically carbapenems, second- and third-generation cephalosporins.*

*Also, in the univariate analysis, the number of antibiotics, types of antibiotics and days of preceding exposure were more strictly related to Porin-ER-Kp strains than KPC-CR-Kp strains.*

Orsi, G.B. et al. Infection (2013) 41:61–67

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## General classification of control strategies for multidrug-resistant organisms

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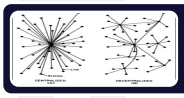
**Horizontal vs Vertical strategies**
- Horizontal: Hand hygiene, decolonization
- Vertical: Active surveillance and contact precautions


**Reactive vs Proactive strategies**
- Reactive: Contact tracing
- Proactive: Active surveillance of high risk patients


**Endemic vs outbreak setting**
- Endemic: Containment will usually be the aim
- Outbreak: Eradication can be the aim



**Coordinated vs individual approach**
- Coordinated: Planning, implementation, monitoring and feedback for all units
- Decentralised: Planning, implementation and monitoring by individual units

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## Elements of multimodal IPC strategy: Ground-level

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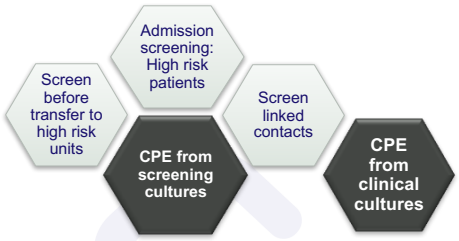


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## Elements of multimodal IPC strategy: Ground-level

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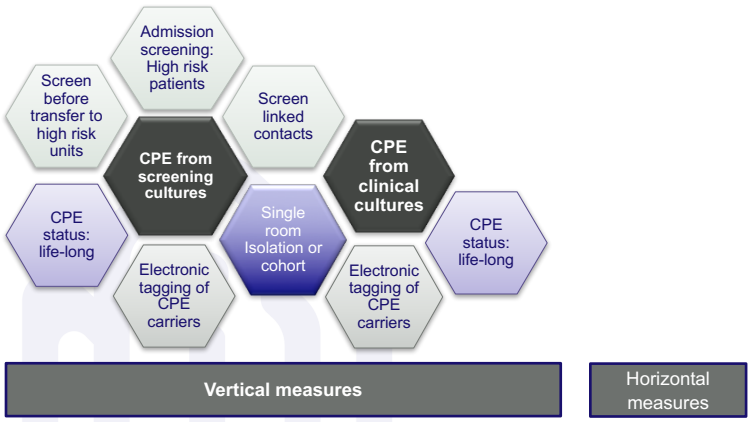


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## Elements of multimodal IPC strategy: Ground-level

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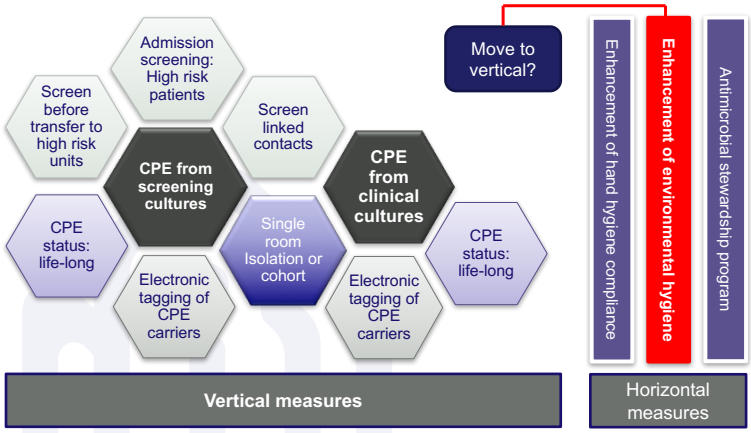


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## Asymptomatic CPE carriers: sources

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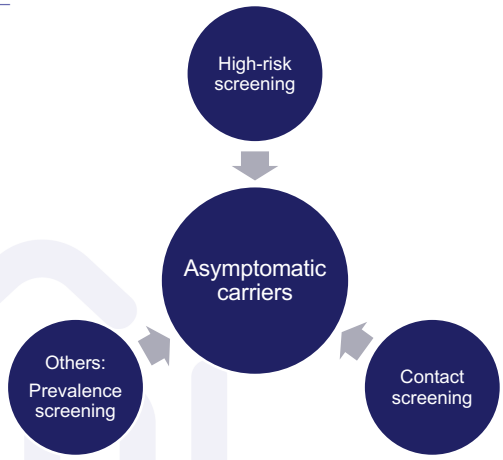


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## Anatomical site and sampling frequency

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- Which anatomical site(s) to screen?
  - No systematic comparative study to identify the most efficacious site(s) to screen
  - Rectum is the commonest anatomical site to be screened
  - If rectal swab cannot be done, then stool can be sent for screening
  - A cross sectional microbiological survey on CRE identification, showed that as a single site, rectum is the best
- How many samples are needed?
  - No systematic studies
  - Most guidelines suggest repeated sampling
  - Most centres do convenience sampling
  - Repeated sampling is probably appropriate for centres

TABLE 2. Sensitivity of Culture of Different Anatomic Sites for *Klebsiella pneumoniae* Carbapenemase–Producing Enterobacteriaceae

| | No. of positive cultures ($N$ = 24) | Sensitivity, % (95% CI) |
|---|---|---|
| Skin sites | | |
| Inguinal | 19 | 79 (58–93) |
| Axillary | 18 | 75 (53–90) |
| Upper back | 6 | 25 (10–47) |
| Antecubital fossae | 6 | 25 (10–47) |
| Nonskin sites | | |
| Rectal[a] | 21 | 88 (68–97) |
| Urine ($N$ = 19)[b] | 10 | 53 (29–76) |
| Oropharyngeal/tracheal secretions | 10 | 42 (22–63) |
| Combined sites | | |
| Rectal and inguinal | 24 | 100 (86–100) |
| Rectal and axillary | 23 | 96 (79–100) |
| Axillary and inguinal | 22 | 92 (73–99) |

NOTE. CI, confidence interval.
[a] Three patients had negative rectal swab cultures but positive cultures of inguinal skin.
[b] Five patients were anuric, so urine was not collected for culture.

Thurlow, C. J. et. al. ICHE 2013

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# Implementing high-risk screening

AUDIT is a MUST!

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**Screening of high-risk patients**

- Implementing high-risk screening
- Implementing screening of epidemiologically-linked patients (contact screening)
- Effectiveness of high-risk screening

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### Issues to consider in implementing high-risk screening

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- Definition of high-risk patients
  - Based on local epidemiology
- Responsibilities must be clearly defined
  1. Who will identify high-risk patients?
  2. How will they identify high-risk patients?
  3. Who will order the test for rectal screening cultures?
  4. Who will collect the rectal screening cultures?
  5. Who will review the results?
  6. Who will take actions on the results?
- Audit the compliance to high-risk screening

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### High-risk patients: definition

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- Guided by local epidemiology
  - Hospitalization in the preceding 1 year (all hospitals)
    - Overseas hospitals
    - Hospitals other than primary institution
    - All hospitals
  - Before and/or transfer to stepdown wards*
  - Before and/or after transfer to intensive care units (ICUs)*
  - Before and/or after transfer to haematology/oncology units*

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## Who will identify high-risk patients

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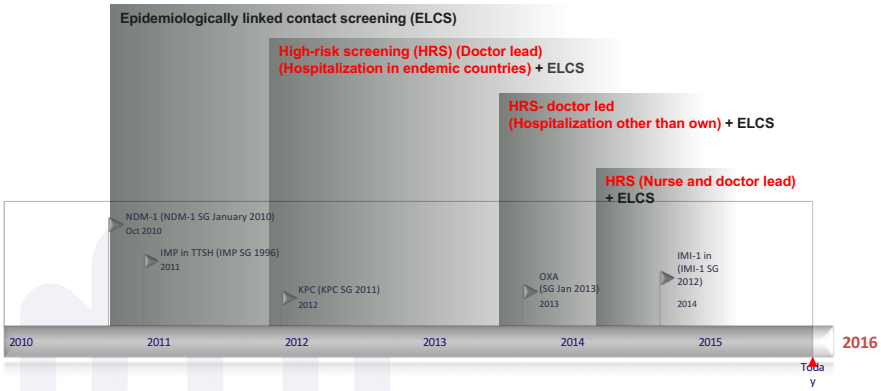


Infection control nurses identified and ensured screening for high-risk patients from January 2018.
Compliance to high-risk screening increased to 95%

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## Who will identify high-risk patients

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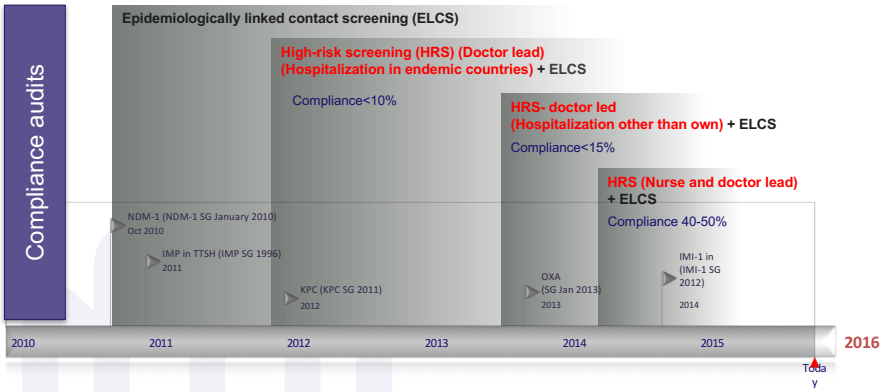


Infection control nurses identified and ensured screening for high-risk patients from January 2018.
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## Identifying high-risk patients

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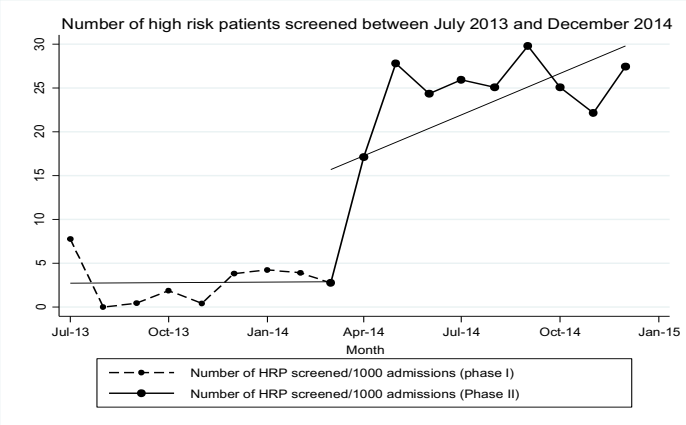


During phase 1 (July 2013–March 2014), surveillance cultures were obtained following physician orders.
During phase 2 (April 2014–December 2014), surveillance culture orders were ordered at the discretion of the nursing staff.
Finding: Significantly more high-risk patients were screened following the intervention in phase 2 than following the intervention in phase 1. The number of CREs identified also increased during phase 2 compared with phase 1, but these numbers were not significantly different.

Chia, G. et al. *Infection control & hospital epidemiology* 37.2 (2016): 238-239.

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## Keeping KPCs away with high risk screening!

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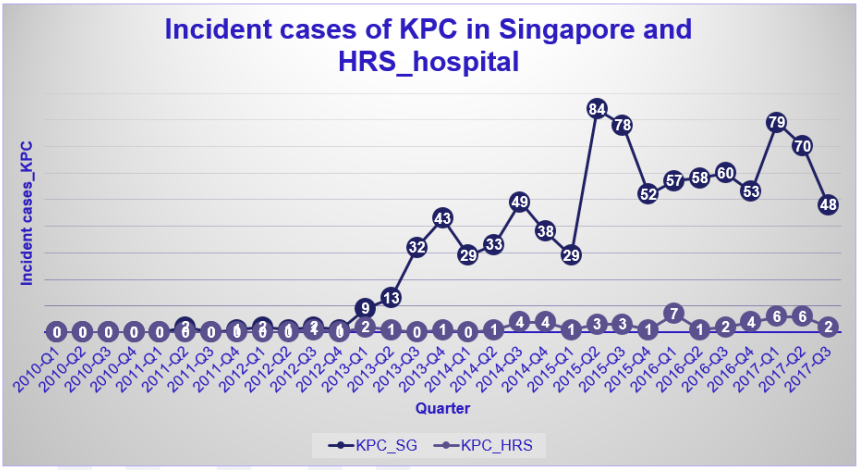


- HRS hospital is endemic for NDM, OXA, IMI, and IMP
- >90% of KPCs identified at HRS hospital are from high-risk screening (HRS)
- HRS hospitals remain free from active circulation of KPC, most probably due to HRS (needs to be scientifically evaluated)

Unpublished data

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# Implementing screening of epidemiologically-linked contacts (Contact screening)

**AUDIT is a MUST!**

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## Contact screening: Main strategy

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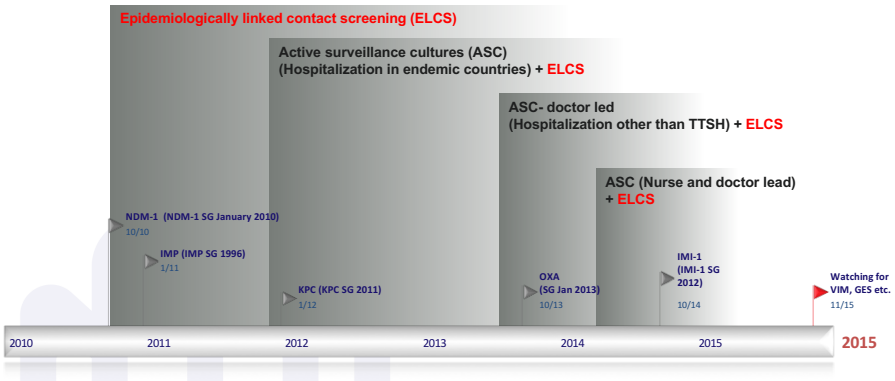


Contact tracing has been part of strategy for CPE control since 2010

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**Issues to consider in implementing contact screening**

- Definition of epidemiologically-linked contacts
  - Usually based on outbreak experience and expert opinion
  - Ease of implementation
  - Risk assessment
    - Involved unit
    - Patient profile
    - Genotype?
    - Bacterial species?
  - Available fund and manpower
- Responsibilities must be clearly defined
  1. Who will identify contacts?
  2. How will they identify contacts?
  3. Who will order the test for rectal screening cultures?
  4. Who will collect the rectal screening cultures?
  5. Who will review the results?
  6. Who will take actions on the results?
- Audit the compliance to high-risk screening

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**Epidemiologically-linked patients (contacts): definition**

- Definition is not widely available
- Revolves around spatial and temporal overlap
- Options for spatial overlap:
  1. Patients sharing the hospital
  2. Patients sharing the same ward
  3. Patients sharing the same room/cubicle
- Options for temporal overlap:
  1. Any duration of overlap in the defined space
  2. Duration of overlap for X number of days
- Example:
  - Who: All patients who overlapped in the same ward with the index patient
  - Risk duration: Date of admission (or date of last negative CPE screen) to date of CPE culture of Index patients
  - Duration of overlap: any duration

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## Contact screening implementation flow

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| | |
|---|---|
| ICN (in-house electronic system) | Identification of index patients |
| ICNs | Generation of list of contacts |
| Ward nurses (prompted by ICNs) | Ordering of tests |
| Ward nurses | Collection of samples |
| ICNs | Review of results |
| ICNs | IPC action and dissemination of information |
| Internal (ICNs) and external (HAI surveillance team) | Compliance audit |

Compliance ranges from 75-90%

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## Effectiveness of CPE control strategies for NDM

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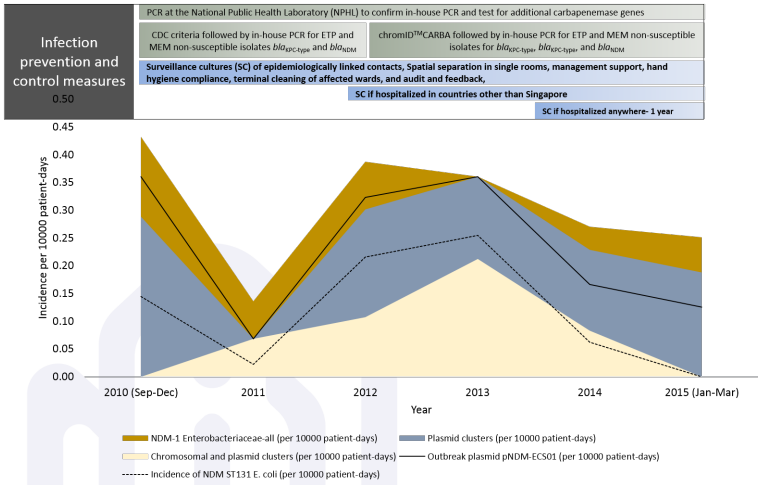


- Clonal transmission of NDM-1 Enterobacteriaceae was controlled with classical IPC methods
- Plasmid mediated transmission is still ongoing

P0783: ECCMID 2018

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## Downside of reactive infection control strategy

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Reactive Infection Control Strategy for Control of New Delhi Metallo-β-Lactamase (NDM)-Producing *Enterobacteriaceae* Analyzed Using Whole-Genome Sequencing: Hits and Misses

Kalisvar Marimuthu, MRCP;[1,2a] Oon Tek Ng, MPH;[1a] Wei Xin Khong, PhD;[1] Eryu Xia, BSc;[3] Yik-Ying Teo, PhD;[3,4,5,6,7] Rick Twee-Hee Ong, PhD;[4] David Chien Lye, FRACP;[1,2] Angela Liping Chow, PhD;[8] Prabha Krishnan, FRCPath;[9] Brenda Sze Ang, MPH[1]

Genetically distinct isolates of New Delhi metallo-β-lactamase (NDM)–producing *Enterobacteriaceae* were identified from the clinical cultures of 6 patients. Screening of shared-ward contacts identified 2 additional NDM-positive patients. Phylogenetic analysis proved that 1 contact was a direct transmission while the other was unrelated to the index, suggesting hidden routes of transmission.

*Infect Control Hosp Epidemiol* 2016;1–4

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# Dissemination of information

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## Information dissemination to the healthcare team

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At the point of identification

Dear all,
**1** patient in **Ward** ___ were tested positive for **Carbapenemase-Producing Enterobacteriaceae (OXA) from rectal swab** sent on **02/05/2018** from high risk screening.
A total of **37** current inpatients have been identified for contact screening.
The following actions are required:

- Send stool/rectal swab x 1 for CRE screening. Ensure fecal matter is visible on swab.
- Order test via CCOE under **Contact screening - CRE (Initiated by ICN).**
- Strict Contact Precautions for all the inpatients undergoing screening - apron & gloves, to change between patient contact and adherence to good hand hygiene.
- Limit the patients' movement except to ACA/HD/ICU or discharge to own home.
- Limit group activities during this period.
- Ensure that all screening results are out before discharging/transferring patients to Nursing Home, BSU, Rehab and other institutions.

For more information, please refer to the CRE FAQ in the Infection Control Webpage:
http:// /Documents/FAQ/CRE%20CPE%20FAQ%20for%20staff.pdf
**Regards,**

**Senior Staff Nurse, Infection Control Unit**
DID:

Follow-up

Dear all,

The contact screening in Ward 7A has been completed.
No current inpatient was found to be CRE positive.

Best Regards,

Senior Staff Nurse, Infection Control Unit, Nursing Service

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## Informing affected patients

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New discharged inpatient CPE to inform

Dear Dr

A patient who was admitted under your care has been diagnosed with New Delhi Metallo-beta-lactamase-1 (NDM-1) producing Enterobacter cloacae from rectal swab.

The details of the patient are given in the table below.

| Name | NRIC | Last Admission | | Ward/Bed before discharge (Last adm) | Inpatient Consultant I/C | Index genotype | Date notification of CRE result | Location where swab is taken | Culture date | Specimen site | Result | Discharge to |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Adm | Discharge | | | | | | | | | |
| | | | | Ward | | | | | | Rectal | NDM-1 | Home |

We would greatly appreciate it if you or one of your team members could call the patient/ spokes-person to inform the result and document the communication in CDOC.

Some of the frequently asked questions by the patient or family members and suggested answers are below.

http:// FAQ/CRE%20CPE%20FAQ%20for%20Clinicians.pdf

If you have further questions, please feel free to e-mail Dr Brenda Ang and Dr Kalisvar Marimuthu.
You can also call/sms Dr Kalisvar at 96451789.

Regards,

Senior Staff Nurse, Infection Control Unit

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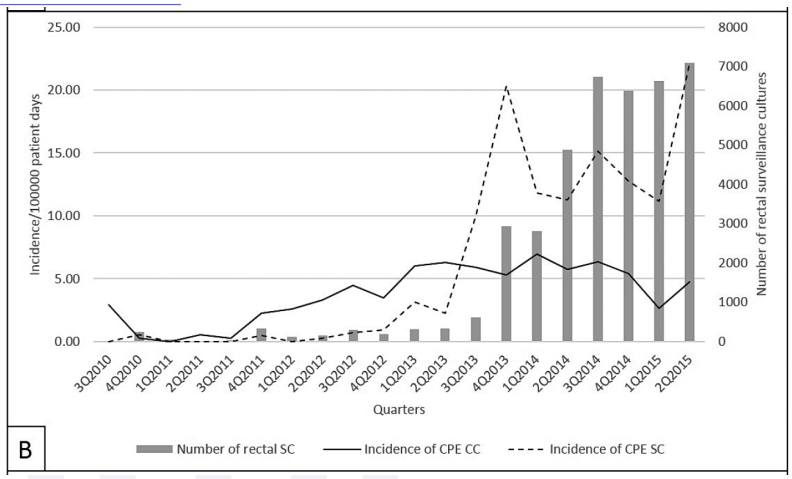
## Effectiveness of identifying asymptomatic carriers




With increasing detection and physical separation of asymptomatic carriers, a decrease in CPE clinical cultures was noted

Kalisvar et al; **CID 2017:64 (Suppl 2)**

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## Downstream impact of CPE identification

- Transfer to rehabilitation facilities
- Transfer to nursing homes
- Discharge to own homes (concerns from families)
- Lack of isolation rooms and problems with cohorting

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## Geographical separation of and contact precaution for CPE carriers

- Geographical separation
- Contact precaution

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## Geographical separation

- Support from hospital management, nursing team, and medical team is critical
- Usually affected by:
  - Bed occupancy rate
  - Availability of single rooms
- Various methods of geographical separation
  - Single room isolation
    - Lack of single rooms
  - Whole ward cohorting
    - Lack of sufficient patients to fill the wards at
  - Nested cohorting within a “clean” ward
    - Risk of transmission to “clean” patients

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## Contact precaution

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- Contact precaution
  - Most international guidelines recommend contact precaution when managing patients with CPE
  - The evidence for benefit is inferred from outbreak control bundles
  - Generally should include:
    - Gown
    - Gloves
    - ± masks
  - Compliance audit is a must but there is a lack of standard audit protocol

More studies are needed

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## Environmental hygiene

- Environmental contamination and CPE
  - Evidence for environment
  - Problematic surfaces
  - Cleaning methods
- Sinks and CPE
  - Burden of proof
  - How to handle sinks?

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## Hidden transmission of CPE: role of hospital environment

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**Methods:**

- Over a 5-year period (2010 to March 2015) all NDM-1-producing Enterobacteriaceae (NDM-E) from a 1700-bed teaching hospital were whole-genome sequenced
- Genomically-linked plasmid-mediated NDM horizontal transmission was defined based on inter-isolate shared plasmids
- Hidden transmission was defined as genomically-linked NDM-positive subjects detected only by clinical cultures and not by surveillance cultures
- Spatiotemporal ward overlap was defined as the contact patient sharing a ward with a known CPE-carrier for at least 24 hours
- Spatial-only ward overlap was defined as the contact patient sharing a ward with a CPE carrier regardless of time overlap

**Results:**

| Factors | Chromosomal clusters (n=35) (%) | Plasmid clusters (n=51) (%) |
|---|---|---|
| Spatial and temporal overlap | 23 (68.6) | 31 (60.8) |
| Hidden transmission | 12 (34.3) | 20 (39.2) |
| Hidden transmission uncovered via: | | |
| Urine culture | 12/12 (100) | 17/20 (85) |
| Blood culture | 0 | 1/20 (5) |
| Other cultures | 0 | 2 (10) |

P1102: ECCMID 2018

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## These pathogens are survivors

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TABLE 1 Survival times and infectious doses retrieved or extrapolated from published studies[a]

| Organism | Survival time | Infectious dose |
|---|---|---|
| Methicillin-resistant *Staphylococcus aureus* | 7 days–>7 mo | 4 CFU |
| *Acinetobacter* | 3 days–>5 mo | 250 CFU |
| *Clostridium difficile* | >5 mo | 5 spores |
| Vancomycin-resistant *Enterococcus* | 5 days–>4 mo | $<10^3$ CFU |
| *Escherichia coli* | 2 h–16 mo | $10^2$-$10^5$ CFU |
| *Klebsiella* | 2 h–>30 mo | $10^2$ CFU |
| Norovirus | 8 h–7 days | <20 virions |

Stephanie J Dancer. Clinical Microbiology Review 2014.

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INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

ORIGINAL ARTICLE

No-Touch Disinfection Methods to Decrease Multidrug-Resistant Organism Infections: A Systematic Review and Meta-analysis

Alexandre R. Marra, MD;[1,2] Marin L. Schweizer, PhD;[3,4,5] Michael B. Edmond, MD[1,6]

- 20 studies were included in the final review
- 13 studies on UVL system and 7 studies on HPV system

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## Summary of the two systems

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| Criteria | UVL system | HPV system |
|---|---|---|
| Number of studies | 13 | 7 |
| Specifics | Pulsed Xenon UVL (n=8)<br>UV-C radiation (n=4)<br>Unspecified (n=1) | Not mentioned |
| Countries | US (n=13) | US (n=4)<br>UK (n=2)<br>Australia (n=1) |
| After terminal cleaning | All studies | All studies |
| Study years | 2011-2014 | 2005-2012 |
| Outcome measures | | |
| CDI rates | 11 (6 high baseline rates) | 6 (2 high baseline rate) |
| MRSA rates | 4 | 3 |
| VRE rates | 4 | 2 |
| MDR Gram-negatives | 2 | 0 |
| HAI rates | 1 | 0 |
| SSI rates | 1 | 0 |

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## HPV for everything…

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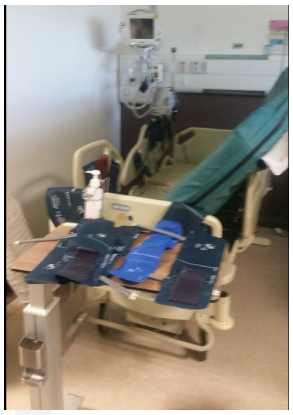

- Average down time 4-7 hours
- And…

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## Walls were allergic to H2O2!

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Beware of the type of paint!

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## Sinks: Can't live without them?

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- Hand hygiene sinks are more commonly implicated than other water sources in healthcare facilities
- Commonly implicated pathogens:
  - *Pseudomonas* sp.
  - Enterobacteriaceae
    - *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Enterobacter species, Citrobacter species*, and *Pantoea agglomerans*
  - Non-fermenters
    - *Stenotrophomonas maltophilia, Acinetobacter baumanii, Elizabethkingia meningoseptica*

Parkes and Hota. Curr Infect Dis Rep (2018) 20: 42

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## Unfavorable design features

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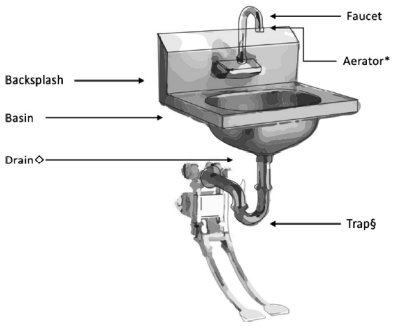


**Fig. 1** Anatomy of a hospital sink and associated nomenclature. *Flow modulator; §U-bend/P-trap/S-trap/Siphon; ◊outlet/strainer; image courtesy of Bryan Graham Huck

- Promotes biofilm formation
- Subsequent disruption of biofilm resulting in spread

Parkes and Hota. Curr Infect Dis Rep (2018) 20: 42

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## IPC strategies: still in the works

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- Cleaning and disinfection/ scaling and disinfection
  - Effectiveness appears temporary
  - Interrupts outbreaks but effect seems to be temporary
  - Disinfectant resistance is a significant problem
- Pressurized steam
  - Short lasting effect for OXA-48
- Self-disinfecting traps
  - Use vibration unit coupled with ultraviolet radiation/heaters
  - Effects were non-sustained in some studies
- Replacement of the sinks and plumbing system
  - Effects were non-sustained

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## Section summary

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- There are two distinct (major) mechanisms of resistance of Enterobacteriaceae to carbapenems: CPEs and NCPCREs
- NCPCRE is associated more with carbapenem exposure than CPE (case for antimicrobial stewardship)
- Acquisition of CPE is probably related more with horizontal transmission (case for infection prevention and control)
- High-risk screening and contact screening coupled with geographical separation is effective in controlling CPEs however, strategized implementation is vital
- Environmental contamination and subsequent onward clonal transmission plays an important role in CPE transmission during outbreaks and non-outbreak setting
- Sink colonization play an important role in CPE transmission to patients

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| | |
|---|---|
| December 13, 2018 | *(FREE Teleclass)*<br>THE BEST WAYS TO GET YOUR HOSPITAL TO TALK ABOUT INFECTION CONTROL<br>Speaker: **Prof. Andreas Voss**, Radboud University, The Netherlands<br><br>**Sponsored by Lonza (www.lonza.com)** |
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