Is there enough evidence from research on plasmid-encoded antimicrobial resistance to change infection control guidelines?

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No disclosures
Infections due to ESBL-harboring *E. coli* in healthcare settings in Europe 2012-2015

Source: EARS-NET
Nosocomial transmission, especially in LTCFs…!

Transmission dynamic for exposed contacts

Pediatric and adult inpatients in Basel hospital
2008 – 2010

<table>
<thead>
<tr>
<th></th>
<th>Klebsiella</th>
<th>E.coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patient</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Exposed patient</td>
<td>24</td>
<td>88</td>
</tr>
<tr>
<td>Transmission events</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Contact precautions</td>
<td>78%</td>
<td>25%</td>
</tr>
<tr>
<td>Incidence</td>
<td>13.8/1000J.</td>
<td>5.6/1000J.</td>
</tr>
</tbody>
</table>

Hilty M et al, Clin Infect Dis 2012

Long term care facilities or rehabilitation centers

9 nursing homes in Sweden, 560 participants
October-november 2008

15 ESBL positive patients in 7/9 nursing homes
14/15 ESBLs = E.coli

Andersson H et al, Scandinavian Journal of Infectious Diseases, 2012
High attack rates during outbreaks...

Typically polyclonal but...

Short-term outbreaks in clinical settings

Karami N., PLOS one, 2013
Influx of ESBL-harbouring *E. coli* into hospitals

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**Table 2.** Univariate and multivariate predictors of extended-spectrum β-lactamase production by *Enterobacteriaceae* causing bacteremia in patients newly admitted to the hospital.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Case patients (n = 38)</th>
<th>Control subjects (n = 72)</th>
<th>OR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Recent events</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current use of antibiotics</td>
<td>9 (24)</td>
<td>5 (7)</td>
<td>4.2 (1.3–13.6)</td>
<td>.02</td>
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<tr>
<td>Bladder catheterization</td>
<td>27 (71)</td>
<td>41 (57)</td>
<td>1.9 (0.8–4.3)</td>
<td>.16</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td>7 (19)</td>
<td>8 (11)</td>
<td>1.8 (0.6–5.4)</td>
<td>.38</td>
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<tr>
<td>Contact with health care system</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Admitted from long-term care facility</td>
<td>16 (42)</td>
<td>10 (14)</td>
<td>4.5 (1.78–11.4)</td>
<td>.001</td>
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<tr>
<td>Hospitalized &lt;3 months before admission</td>
<td>23 (61)</td>
<td>35 (49)</td>
<td>1.6 (0.7–3.6)</td>
<td>.32</td>
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<tr>
<td>Multivariate analysis</td>
<td></td>
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<td></td>
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<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td>2.57 (1.08–6.12)</td>
<td>.03</td>
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<tr>
<td>Admitted from long-term care facility</td>
<td></td>
<td></td>
<td>4.76 (1.82–12.4)</td>
<td>.001</td>
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</table>

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Movement of ESBL genes across enterobacterial genera: within hospital spread

Transmission of ESBL CTX-M resistance

- **E. Coli ST131 CTX-M15**
  - Early 2000’s

- **CTX-M**

- **ESBL-Enterobacter**

- **ESBL-K. pneumoniae**
  - Nowadays

- **blaCTX-M-15**-encoding multiresistance cassette integrated in the pKPN3 K. pneumoniae plasmid backbone
- Recombination points in an IS26 element!
Intra-patient evolution of ESBL-harbouring *E. coli*: community versus hospital acquisition
Slide withheld at request of author
Slide withheld at request of author
ESCMID eLibrary

Slide withheld at request of author
Particular threat: \textit{E. coli} ST131 H30-Rx

Common in long-term care facilities

Cross-sectional study (2 LTCFs, USA)

- 133 samples analysed
- 33/133 FQ-R \textit{E. coli}
- 32/33 FQ-R \textit{E. coli} ST131 H30 subclone
- 9/32 \textit{E. coli} ST131 H30 Rx subset

\textit{Burgess M.J et al., open forum infect dis, 2015}
Carbapenemase-producing Enterobacteriaceae in Europe, 2013

Figure 3: Occurrence of carbapenemase-producing Enterobacteriaceae in 38 European countries based on self-assessment by the national experts, March 2013

Epidemiological stages:
- No cases reported
- Sporadic occurrence
- Single hospital outbreak
- Sporadic hospital outbreaks
- Regional spread
- Inter-regional spread
- Endemic situation
- Data not available
- Not participating
- Uncertain

Source: Interim result report, EUSCAPE, ECDC
Distribution of carbapenemases in Europe, 2013

Figure 5. Occurrence of carbapenemase-producing Enterobacteriaceae by type of carbapenemases in 38 European countries based on self-assessment by the national experts, March 2013

Epidemiological stages
- No cases reported
- Sporadic occurrence
- Single hospital outbreak
- Sporadic hospital outbreaks
- Regional spread
- Inter-regional spread
- Endemic situation
- Data not available
- Not participating
- Uncertain

Source: Interim result report, EUSCAPE, ECDC
Movement of \( \text{bla}_{KPC} \) across enterobacterial genera in hospitals…

Transmission of KPC

\( \text{bla}_{KPC-3} \) harbouring non-ST258 K. pneumoniae

\( \text{E. coli} \)

\( K.\text{pneumoniae} \)

\( \text{Enterobacter spp.} \)

Multiclonal dispersal of KPC genes following the emergence of non-ST258 KPC-producing \textit{Klebsiella pneumoniae} clones in Madrid, Spain

Patricia Ruiz-Garbajosa\(^1\*\), Tania Curiao\(^1,2\), Marta Tato\(^1\), Desirèe Gijón\(^1\), Vicente Pintado\(^3\), Aránzazu Valverde\(^1,4\), Fernando Baquero\(^1,2,5\), María Isabel Morosini\(^1\), Teresa M. Coque\(^1,2,5\) and Rafael Cantón\(^1,5\)
... and in patients under antimicrobial therapy

Risk factors for plasmid transfer:
Critical illness and recent receipt of β-lactam agents other than carbapenems

<table>
<thead>
<tr>
<th>Age (year)/sex</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61/M</td>
<td>63/M</td>
<td>96/M</td>
<td>52/M</td>
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<tr>
<td>Strain</td>
<td>K. pneumoniae 1-S</td>
<td>K. pneumoniae 1-R</td>
<td>K. pneumoniae 2-S</td>
<td>K. pneumoniae 2-R</td>
</tr>
<tr>
<td></td>
<td>M. morganii-S</td>
<td>M. morganii-R</td>
<td>E. aerogenes-S</td>
<td>E. aerogenes-R</td>
</tr>
<tr>
<td>Time from hospitalization to bacterial isolation (d)</td>
<td>6</td>
<td>29</td>
<td>224</td>
<td>231</td>
</tr>
<tr>
<td>Antibiotics use before bacterial isolation</td>
<td>CXM</td>
<td>CXM; CED</td>
<td>CAZ; AK; SCF</td>
<td>CAZ; LEV</td>
</tr>
<tr>
<td>Source</td>
<td>Urine</td>
<td>Urine</td>
<td>Sputum</td>
<td>Sputum</td>
</tr>
<tr>
<td>STb</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Minimum inhibitory concentrations (μg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.25</td>
<td>8</td>
<td>0.125</td>
<td>32</td>
</tr>
<tr>
<td>Mecpenem</td>
<td>0.5</td>
<td>16</td>
<td>0.25</td>
<td>32</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>16</td>
<td>32</td>
<td>128</td>
<td>128</td>
</tr>
</tbody>
</table>

\*CXM, cefuroxime; CED, cefadroxil; CAZ, ceftaziaime; AK, amikacin; SCF, ceftazopen-subactam; MEM, meropenem; TGC, tigecycline; LEV, levofloxacin.

\*NA, not applicable.
WGS-based surveillance to identify the hospital mobilome in Carbapenem-resistant Enterobacteriaceae

KPC-2, -3, and -4 and OXA-48 harbored within many transposons including Tn4401 isoforms on >10 distinct plasmids and as chromosomal insertions

Limited outbreaks against a broader 3-year period of sporadic external entry of many different strains and resistance vectors into the hospital
Parameters regulating horizontal gene transfer

- Factors influencing conjugation of four plasmids
  - pKpQIL: 114 kb, outbreak isolate
  - pKPC-47e: 50 kb, IncN replicon, isolated from patients and the environment
  - pKPC_UVA01: outbreak isolate, nontypeable 43 kb with known transfer to at least 10 different species from seven genera (‘promiscuous’)
  - pKPC_UVA02: outbreak and surveillance isolate, nontypeable 113 kb, transfer to fewer species than pKPC_UVA01
- Temperature: $37^\circ C > 25^\circ C$
- Substrate: broth > filter matings
- Recipient strains: $E. coli < K. pneumoniae$

Non-exhaustive set of 77 genes associated with plasmid transfer, replication, or maintenance showed striking differences between the plasmids: complex mechanisms
Compensatory evolution stabilizes a bacteria–plasmid association

MacLean RC & San Millan A. Current Biology, 2015
Barriers to plasmid adaptation in new clinical bacterial hosts

- Influence of plasmid acquisition on
  - growth rate
  - overall stability
  - evolutionary potential
  - genetic adaptations

Plasmid acquisition leads to a reduction in maximum growth rate relative to the plasmid-free ancestor
Adaptive evolution of plasmid under antibiotic pressure in new clinical bacterial hosts

Adaptive evolution under antibiotic pressure increases stability of pKP33 and reduces plasmid cost in E. coli hosts
Host–specific IS-mediated plasmid deletions underlie adaptive evolution in new clinical bacterial hosts

- Plasmid gene reduction consistently targeted the conjugation machinery
  - Compensatory mechanism to decrease biological cost of plasmid carriage
- Radical restructuring narrows the plasmid host range by constraining its dissemination
  - Tradeoff between horizontal and vertical plasmid transfer
- In the right host background, makings of a potential MDR superbug!!
Transmission from other patients, colonized in the GI tract or infected, sinks, ventilators, and as yet unknown routes…
Risk factors for nosocomial acquisition of KPC producing *K. pneumoniae* (in an outbreak setting)

Table I

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multi-variate analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>23.58</td>
<td>4.91–113.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;28 days in the last 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central line catheterization</td>
<td>15.43</td>
<td>2.74–86.89</td>
<td>0.002</td>
</tr>
<tr>
<td>in the last 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior colonization with VRE</td>
<td>6.00</td>
<td>1.55–23.19</td>
<td>0.009</td>
</tr>
</tbody>
</table>

VRE, vancomycin-resistant enterococci; OR, odds ratio; CI, confidence interval.

Table II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multi-variate analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay</td>
<td>52.91</td>
<td>9.65–290.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;28 days in the last 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central line catheterization</td>
<td>12.64</td>
<td>2.50–64.03</td>
<td>0.002</td>
</tr>
<tr>
<td>in the last 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any exposure to broad-spectrum antibiotic in the last 30 days</td>
<td>7.39</td>
<td>1.36–40.20</td>
<td>0.021</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
Major sources of KPC producing *K. pneumoniae* during outbreaks, 2001-2012

- Sites of infection
- Sites of colonization
**E. coli** may cause relevant environmental contamination in healthcare settings

Easy colonisation of perianal and inguinal regions and therefore frequently used surfaces (toilet seats could serve as reservoirs)

- 1'767 patients
- 286 beds
- 68% of units equipped with bedpan washer-disinfector
- 71% of units with bedpans were rinsed before disinfection

Huttner B., JAC, 2013 - 61% of the beds had shared toilets - 43% of the toilets were equipped with hand sprayers (a spray used to wash bedpans in patients' restrooms, favouring the spread of faecal material)

- 33 ESBL-E carriage (20.6%)
- 32/33 ESBL-P *E. coli*

21 carriers (13%) of 1 specific clone: *E. Coli* BlaCTX-M1-15 ST131

Excreta management in hospitals of 28 Assistance Publique-Hôpitaux de Paris

- 536 Units
- 1'767 patients (13%)
- 68% of units equipped with bedpan washer-disinfector
- 71% of units where bedpans were rinsed before disinfection

M. Lepainteur, Journal of Hospital Infection, 2015

Heavily contaminated surfaces (bedside commode, kitchen, microwave, toilet seat)

<table>
<thead>
<tr>
<th>Table 3: Multiple Logistic Regression Analysis Using the Conditional Maximum Likelihood Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P Value</strong></td>
</tr>
<tr>
<td>Single room occupancy</td>
</tr>
<tr>
<td>Fecal incontinence</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Contamination level per 10% increase</td>
</tr>
<tr>
<td>Bathroom</td>
</tr>
<tr>
<td>Microwave (kitchen)</td>
</tr>
<tr>
<td>Scullery</td>
</tr>
<tr>
<td>Washing bowl</td>
</tr>
</tbody>
</table>

Willemsen I., Infection control & Hospital Epidemiology, 2015
How long do nosocomial pathogens persist on inanimate surfaces?  
A systematic review  
Axel Kramer*1, Ingeborg Schwebke2 and Günter Kampf1,3

<table>
<thead>
<tr>
<th>Type of bacterium</th>
<th>Duration of persistence (range)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td>3 days to 5 months</td>
<td>[18, 25, 28, 29, 87, 88]</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>3 – 5 days</td>
<td>[89, 90]</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>up to 6 days</td>
<td>[91]</td>
</tr>
<tr>
<td>Clostridium difficile (spores)</td>
<td>5 months</td>
<td>[92–94]</td>
</tr>
<tr>
<td>Chlamydia pneumoniae, C. trachomatis</td>
<td>≤ 30 hours</td>
<td>[14, 95]</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>15 days</td>
<td>[90]</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td>7 days – 6 months</td>
<td>[90, 96]</td>
</tr>
<tr>
<td>Corynebacterium pseudotuberculosis</td>
<td>1–8 days</td>
<td>[21]</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1.5 hours – 16 months</td>
<td>[12, 16, 17, 22, 28, 52, 90, 97–99]</td>
</tr>
</tbody>
</table>
### Current infection control guidelines for MDR GNB

<table>
<thead>
<tr>
<th></th>
<th>Hand hygiene</th>
<th>Contact precautions</th>
<th>Single room</th>
<th>Cleaning / disinfection</th>
<th>Environmental screening</th>
<th>Antimicrobial stewardship</th>
<th>Active surveillance cultures</th>
<th>Note flagging / alert code</th>
<th>Cohort patients</th>
<th>Cohort staff</th>
<th>HCW screening</th>
<th>Patient decolonisation</th>
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<tbody>
<tr>
<td><strong>ESBL-E</strong></td>
<td>All</td>
<td>Outbreak</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
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<tr>
<td><strong>CPE</strong>*</td>
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<td></td>
<td>HPS (Scotland)</td>
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<td>ECDC</td>
</tr>
</tbody>
</table>
Usefulness of contact precautions

What are the precautions?

• **Vertical approach**
  - Active surveillance culture
  - **Contact precautions** for colonized/infected patients
  - Decolonization of patients with specific MRB

• **Horizontal approach**
  - **Standard precautions/hand hygiene**
  - Universal decolonization (Chlorhexidine bathing)
  - Universal use or gloves/gowns
  - Antimicrobial stewardship
  - Environmental cleaning and disinfection

- Hand hygiene after a contact with the environment
- Single room or cohorting
- Signaling
- Screening in case of outbreaks
- Hand hygiene
- Gloves & apron if projection risk
- Mask if aerosolization risk
Usefulness of contact precautions

Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial

Lennie P G Derde, Ben S Cooper, Herman Goossens, Surbhi Malhotra-Kumar, Rob J L Willems, Marek Gniadkowski, Waleria Hyrniewicz, Joanna Ernpe, Mirjam J D Dautzenberg, Djillali Annane, Irene Arogão, Annie Chalfine, Ugo Dumpis, Francisco Esteves, Helen Giamarello, Igor Muzlovic, Giuseppe Nardi, George L Petrikkos, Viktorija Tomic, Antonio Torres Marti, Pascal Stammet, Christian Brun-Buisson*, Marc J M Bonten*, on behalf of the MOSAR WP3 Study Team

- MDRO reduction by hand hygiene program plus Chlorhexidine body washes
- Mainly caused by reduction in MRSA acquisition, not MDR-GNB
- Screening and isolation did not reduce acquisition rates of MDROs
Impact of cessation of contact precautions on transmission of ESBL-harbouring *E. coli*

Sarah Tschudin-Sutter, Reno Frei, Friedbert Schwahn, Milanka Tomic, Martin Conzelmann, Anne Stranden, Andreas F. Widmer

After contact precautions were discontinued, we determined nosocomial transmission of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* by screening hospital patients who shared rooms with ESBL-producing *E. coli*-infected or -colonized patients. Transmission rates were 2.6% and 8.8% at an acute-care and a geriatric/rehabilitation hospital, respectively. Prolonged contact was associated with increased transmission.
### Containment measure for KPC-producing *K. pneumoniae* outbreaks

Table 2
Intervention measures implemented by health facilities to contain KPC-producing *Klebsiella pneumoniae* outbreaks, 2001–2012

<table>
<thead>
<tr>
<th>Reference</th>
<th>Contact precautions</th>
<th>Patient isolation</th>
<th>Culture surveillance</th>
<th>Exclusively for patient care</th>
<th>Further environmental cleaning</th>
<th>Training*</th>
<th>Employee monitoring</th>
<th>Cultures of environmental surfaces</th>
<th>Effectiveness of measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souli et al 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Agodi et al 2011</td>
<td>Yes</td>
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<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbonne et al 2009</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Robustillo Rodela et al 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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KPC, *Klebsiella pneumoniae* carbapenemase; NR, not reported.

*Training and informative meetings between officials.*
Isolation measures may have direct and indirect benefits on cross-transmission.

**Direct benefits**
- Single room
- Dedicated, individual toilets (better management of excreta)

**Indirect benefits: Compliance with hand hygiene**
- **No contact precautions**
  - Hand hygiene overall: 28%
- **Contact precautions**
  - Hand hygiene overall: 43%

  - Before care: 55%
  - After care: 60%

  - 36'803 opportunities for HH

  - 1619 opportunities for hand hygiene

  **Golan Y, Clin Infect Dis, 2006**

  **Venier AG et al, J Hosp Infect 2012**
Patient education and co-operation are crucial

<table>
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<th>Seven Important Things To Protect Yourself While In the Hospital</th>
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<tbody>
<tr>
<td>Please take the initiative to ask ward staff to perform hand hygiene before touching you</td>
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**PREVENT ILLNESS FROM INTAKE**

- Hand hygiene before meals
- Hand hygiene before medications
- Wipe water tap handle with a wetted disinfectant tissue before getting water for mouth rinsing/tooth brushing

**PREVENT ILLNESS FROM THE TOILET**

- Wipe the toilet seat with disinfectant wetted tissue before use
- After defecation, wash hands with soap and water; then disinfect hands with alcohol handrub. After urination, as usual, wash hands with soap and water
- After defecation using a bedpan, please use a wet tissue to wipe hands; then ask ward staff to provide alcohol handrub to disinfect hands

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*Figure 7* Bedside poster to remind patients about infection control on personal protection from hospital-acquired infections.

*Figure 8* Education pamphlet for self-protection during antibiotic therapy.

While taking antibiotic which is necessary to cure your infection, the antibiotic also kills the normal bacteria in your body and predisposes you to acquire more resistant bacteria.

Therefore, you should enhance personal hygiene by:
- Practise frequent hand hygiene
- Eat or drink only thoroughly cooked or boiled items
- Disinfect and cover all wounds
- Wear mask if you have respiratory infection symptoms
- Young children with symptoms of infection should minimize contact with other children
In conclusion

- Settings with high MDR-GNB (ESBL-E.coli/CR-KPN) colonization pressure, extended hospital stay and close contact between vulnerable patients may serve as amplification platforms to accelerate transmission events.
- Impact of MDR-GNB loads on transmission events remains unclear.
- There are potentially more transmissible and virulent strains that may require contact precautions.
- The contribution of transmission of plasmids rather than strains to ongoing ESBL/Carbapenemase-transmission is currently elusive.

• ➔ Such considerations may favor contact precautions for patients colonized or infected with MDR-GNB.
In conclusion (2)

• When abandoning contact precautions for carriers, a few pre-requisites need to be fulfilled:
  – high compliance with standard precautions including hand hygiene
  – ongoing surveillance and early detection of nosocomial MDR-GNB outbreaks
  – if possible, sporadic molecular typing of infection isolates to exclude ongoing nosocomial transmission of virulent and presumably highly transmissible ESBL-E.coli ST131-H30 and ST258-KPN clones