Carbapenem-Resistant *Enterobacteriaceae*

Patcharasarn Linasmita MD
Infectious Diseases Unit
Srinakharinwirot University

Enterobacteriaceae

- A large family of Gram-negative bacteria

~80 – 95%

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

- *Proteus spp., Morganella spp., Providencia spp.*

Carbapenem Antibiotics

- Imipenem, meropenem, ertapenem, doripenem
- retain activity against the chromosomal cephalosporinases (**AmpC**) and extended-spectrum beta-lactamases (**ESBL**)
  - found in many gram-negative pathogens
    - *Enterobacteriaceae*
      - *Klebsiella pneumoniae*
      - *Escherichia coli*

Carbapenem Resistance

- Organisms are likely multidrug-resistant
- Many different mechanisms
  - Carbapenemases
    - carbapenem-hydrolyzing beta-lactamases
      - Classes A, B, and D are of greatest clinical importance among nosocomial pathogens
    - **carbapenemase-producing CRE (CP-CRE)**
      - are currently believed to be primarily responsible
  - Impaired permeability due to porin mutation

Class A Beta-Lactamase

- require an active-site serine at position 70
- Chromosomally-encoded carbapenemases
  - SME (*Serratia marcescens* enzyme)
  - NMC (non-metalloenzyme carbapenemase)
  - IMI (imipenem-hydrolyzing beta-lactamases)
- Plasmid-encoded carbapenemases
  - KPC (*Klebsiella pneumoniae* carbapenemase)
  - GES (Guiana extended spectrum)

Klebsiella pneumoniae Carbapenemase (KPC)

- The most clinically important of the **Class A** carbapenemases
- reside on transmissible plasmids
- can be transmitted from *Klebsiella* to
  - *E. coli*, *Pseudomonas aeruginosa*, *Citrobacter*, *Salmonella*, *Serratia*, *Enterobacter* spp
- Inhibited by boronic acid

KPC

- First described in a clinical isolate of *K. pneumoniae* in the late 1990s in North Carolina
- KPC-2
  - an enzyme later found to be identical to the initially described KPC
- KPC-3
  - differs from KPC-1/KPC-2 by a single amino acid)
- KPC-possessing isolates have also been increasingly recovered from other regions of the world

Class B Beta-Lactamase

- the metallo-beta-lactamases (MBLs)
  - require **zinc** for efficient hydrolysis of beta-lactams
- can be inhibited by EDTA (an ion chelator)
- Naturally occurring MBLs are chromosomally encoded
  - *Aeromonas hydrophilia*, *Chryseobacterium* spp., *Stenotrophomonas maltophilia*
- Acquired MBLs consist of genes encoded on integrons residing on large plasmids
  - transferable between both species and genera

Metallo-beta-lactamases (MBLs)

- Were initially described in Japan in 1991
- NDM-1 was first described in December 2009 in a K. pneumoniae isolate from a Swedish patient who had been hospitalized in India

New Delhi metallo-beta-lactamase (NDM-1)

- First described in December 2009 in a Swedish patient hospitalized in India with an infection due to *Klebsiella pneumoniae*
- The gene is located in a very mobile genetic element
- Bacteria containing NDM-1 have tested susceptible to colistin or tigecycline
  - such susceptibility may be short-lived
- NDM-1 has also been identified in
  - *E. coli*, *Enterobacter cloacae*
  - non-Enterobacteriaceae (ie *Acinetobacter*)

Class D Beta-lactamase

- OXA-type enzymes
  - preferential ability to hydrolyze oxacillin
    - (rather than penicillin)
- variably affected by the beta-lactamase inhibitors
- OXA-48-type carbapenemases might not exhibit resistance to **third**-generation cephalosporins (ceftazidime)

Carbapenemase-producing organisms

- Carbapenemase-producing organisms can arise from previously carbapenemase-negative strains
  - by acquisition of genes from other bacteria

Carbapenem Resistance

- No **phenotypic** definition will perform perfectly in distinguishing between **CP-CRE** and **non-CP-CRE**

Risk factors

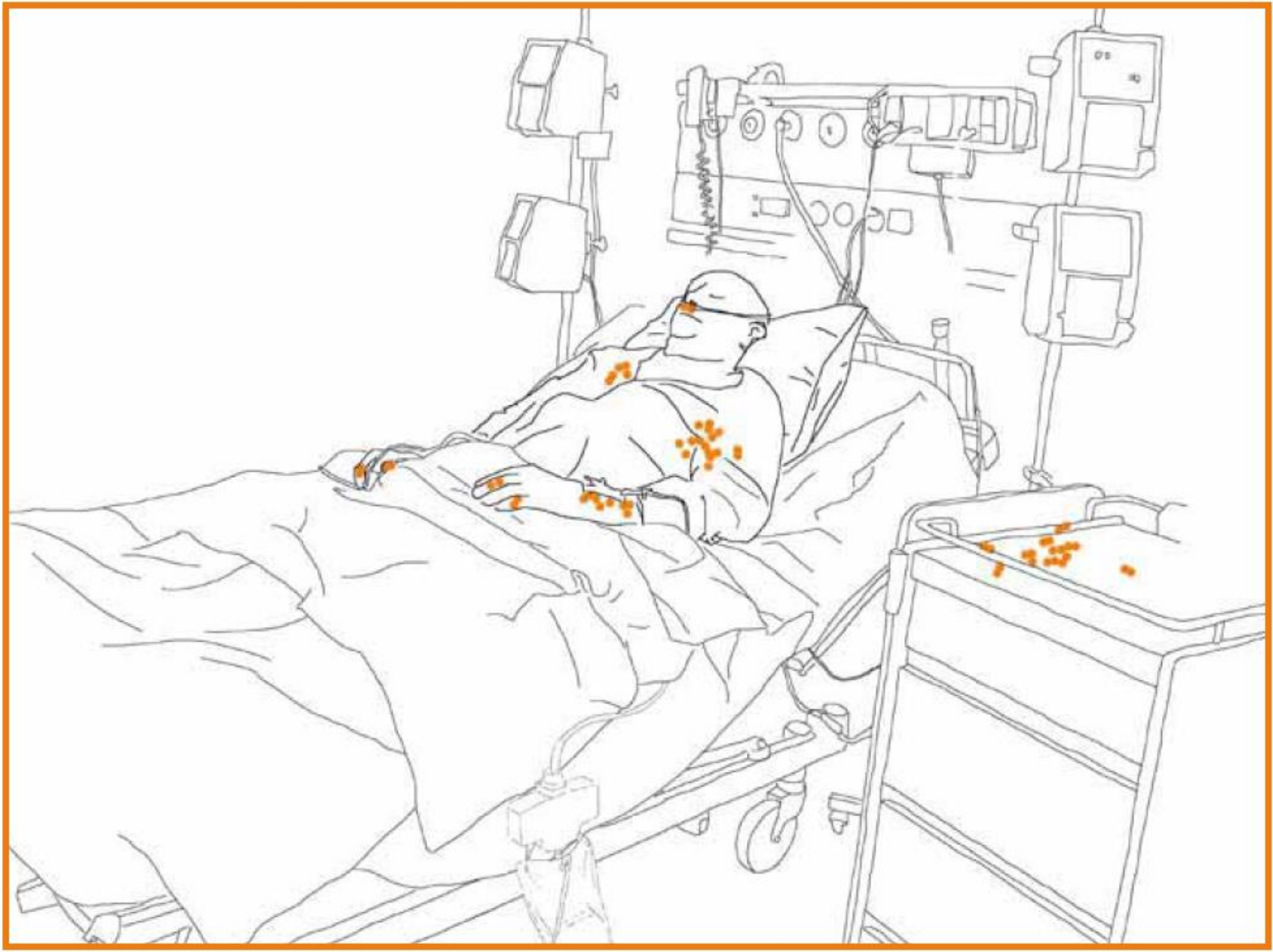
- Use of broad spectrum **cephalosporins** and/or **carbapenems** is an important risk factor for the development of colonization or infection with Carbapenemase-producing organisms
- Reported **carbapenem** use among patients prior to the isolation of **MBL** varies from 15 to 75 percent

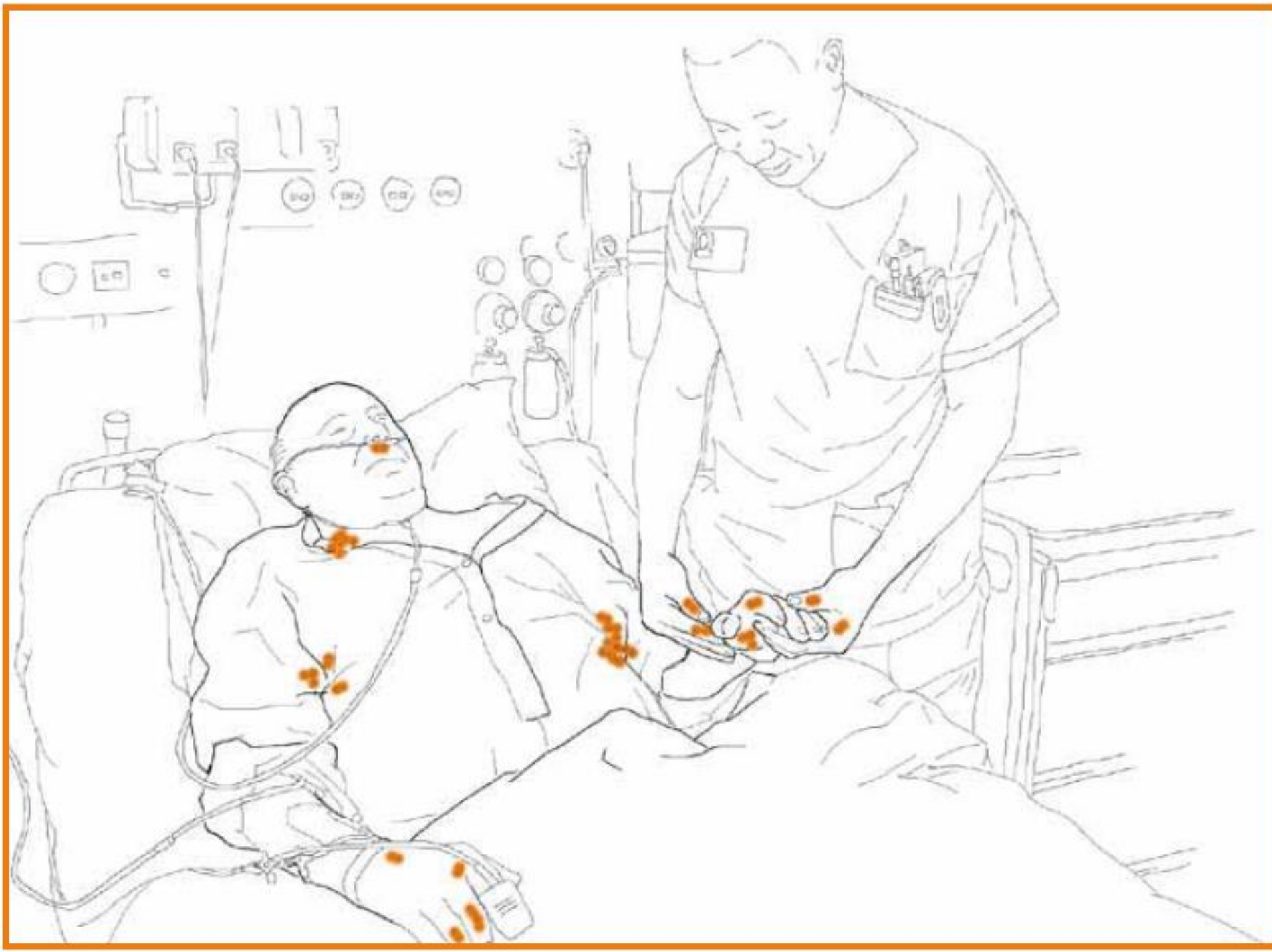
Risk factors

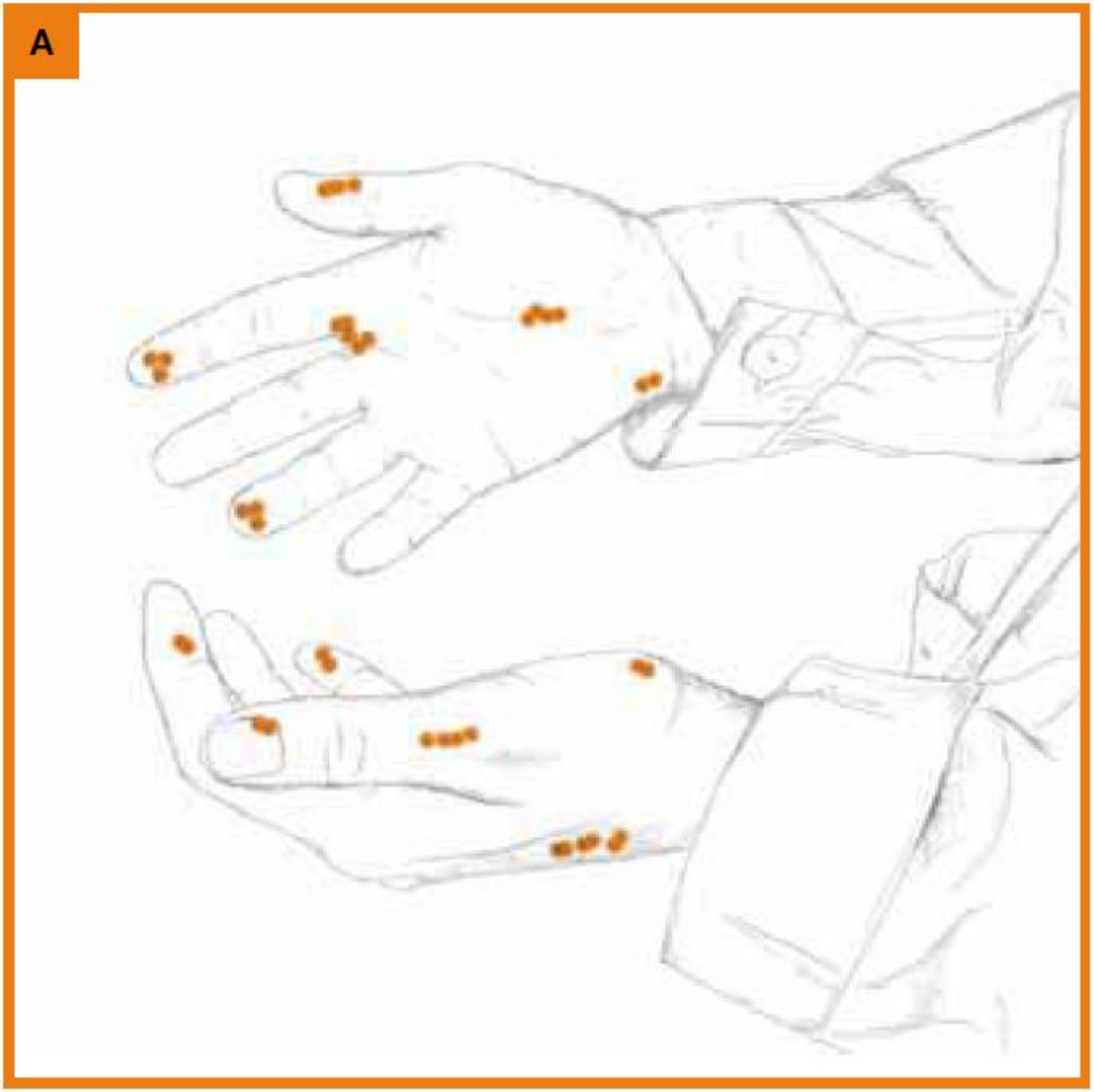
- trauma
- diabetes
- malignancy
- organ transplantation
- mechanical ventilation
- indwelling urinary or venous catheters
- overall poor functional status or severe illness
- received medical care in India and Pakistan
  - NDM-1

Transmission

- to other isolates and genera of bacteria via mobile genetic element
  - transposon, plasmid
- Patients themselves - intestinal colonization
  - reservoir for resistant Enterobacteriaceae
- person to person transmission
  - contact
- from environment reservoir
  - Sink, stethtoscope
  - NDM-1-positive bacteria have been identified in public water supplies in India



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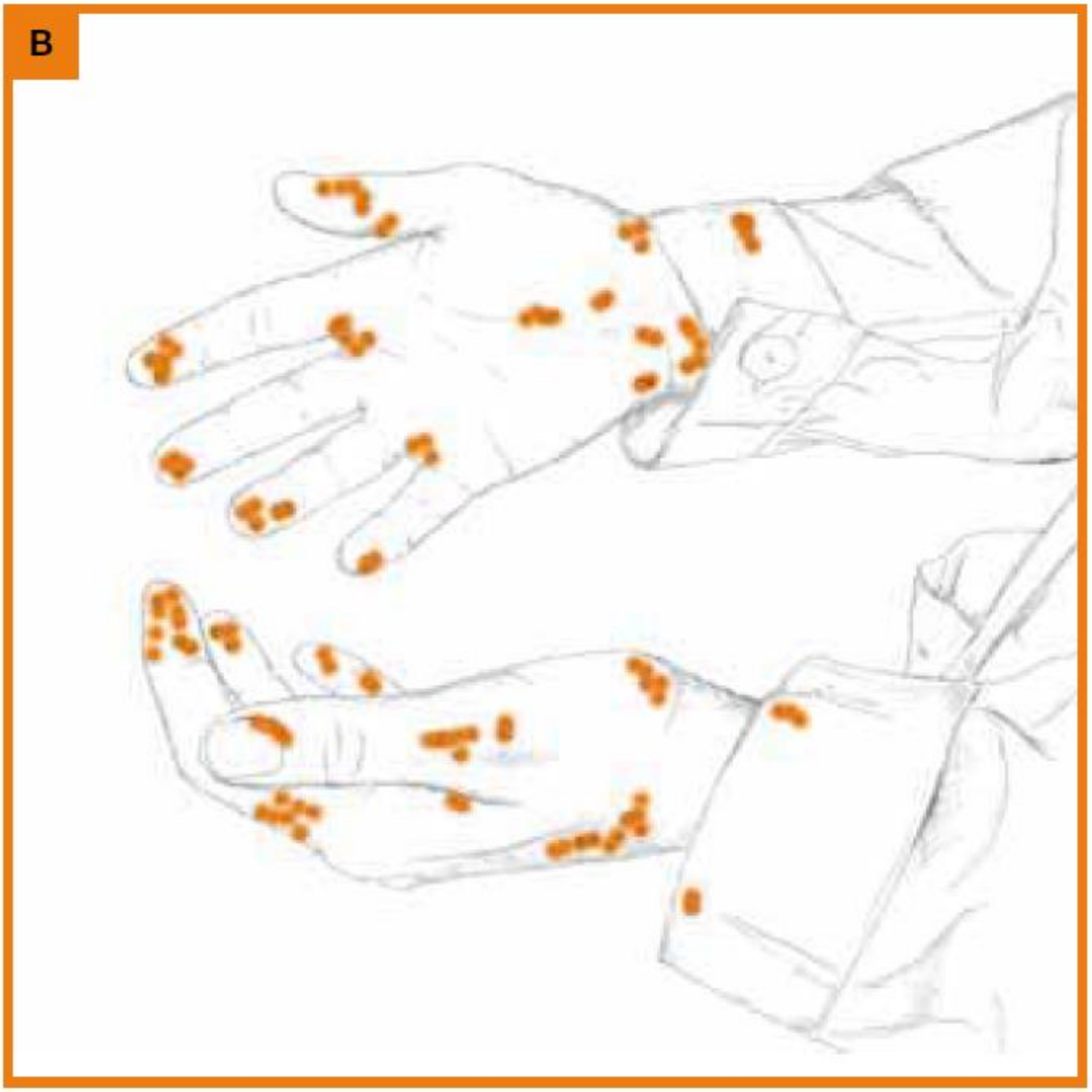
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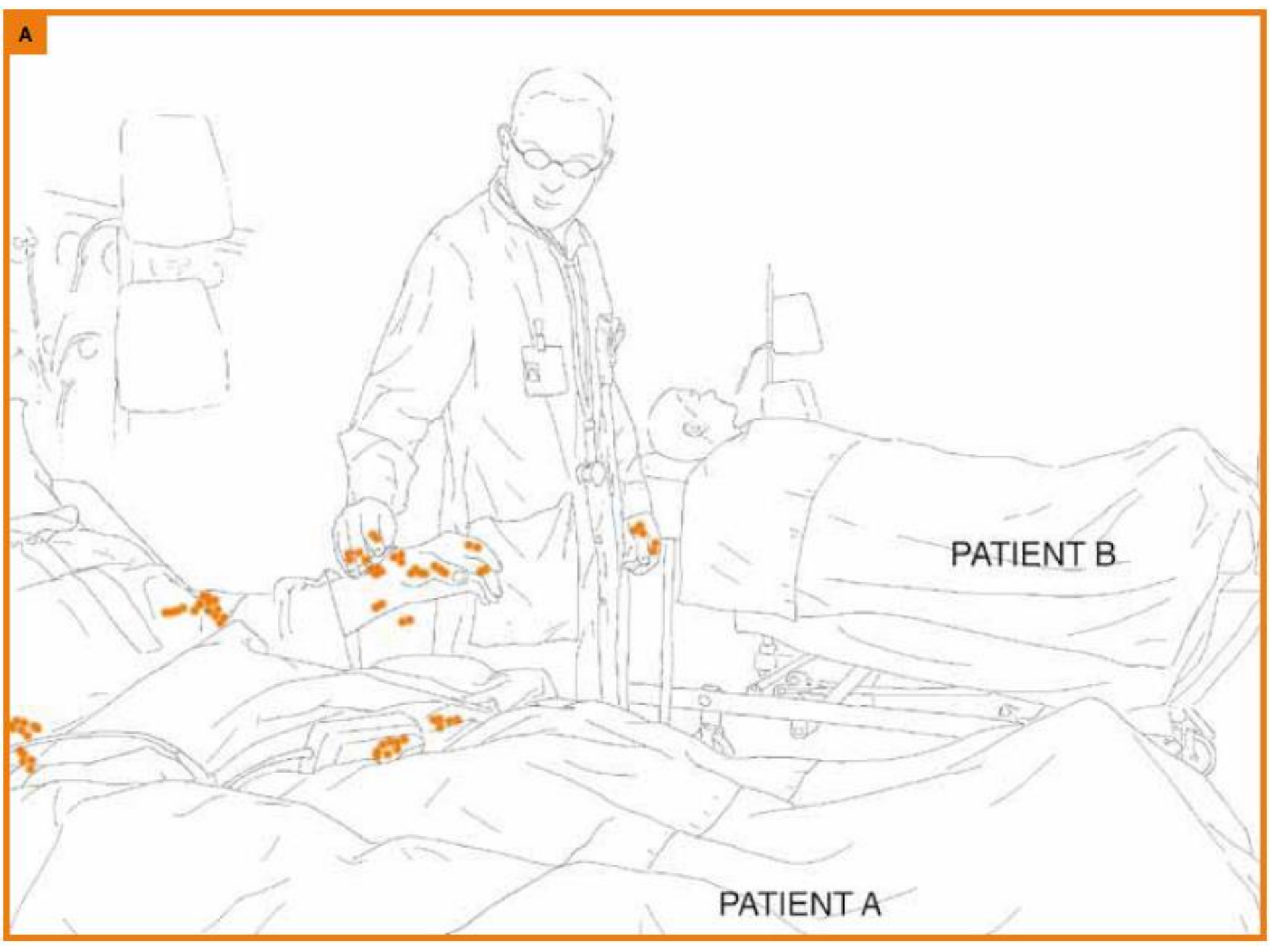
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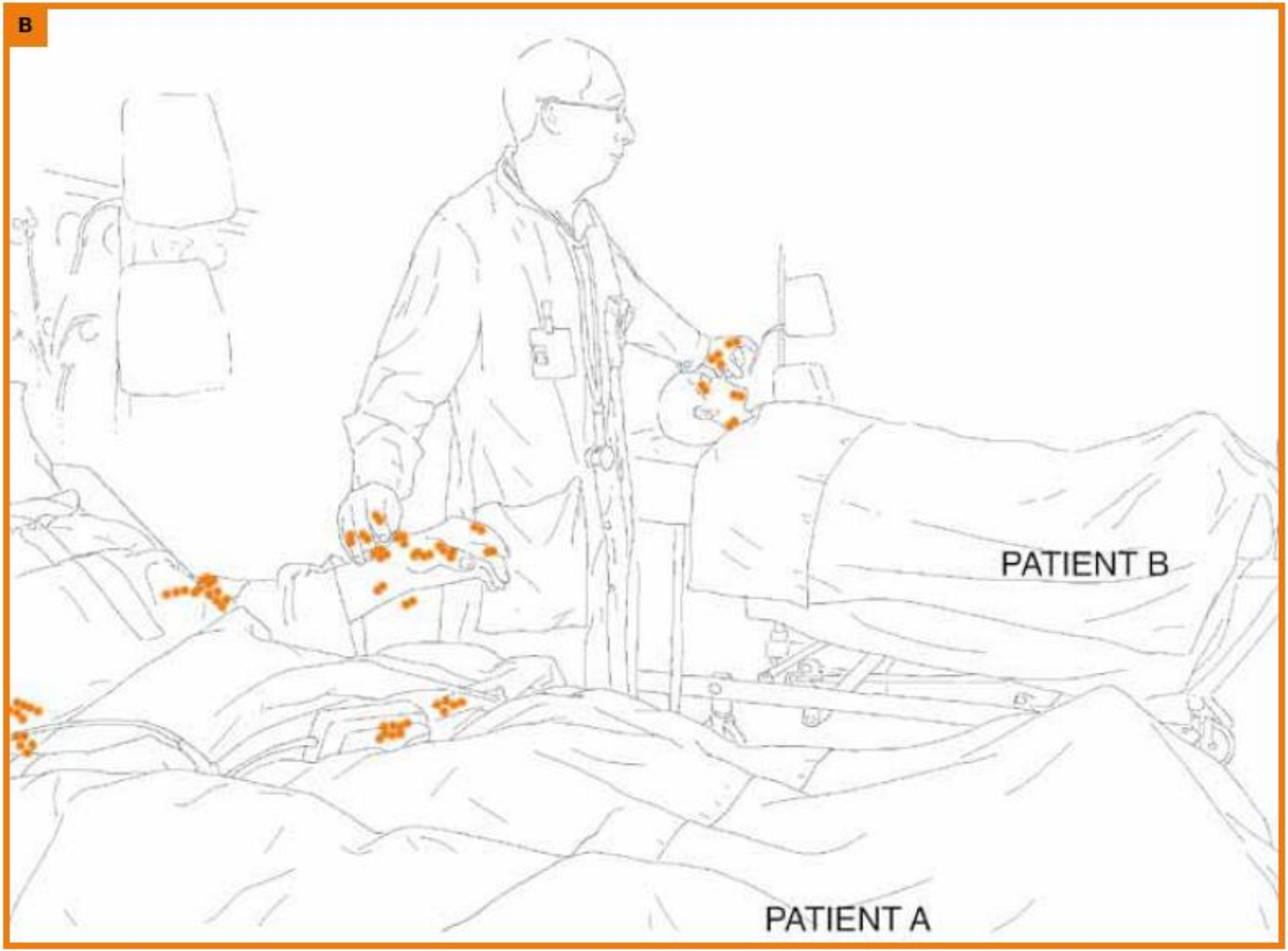
PATIENT B
PATIENT A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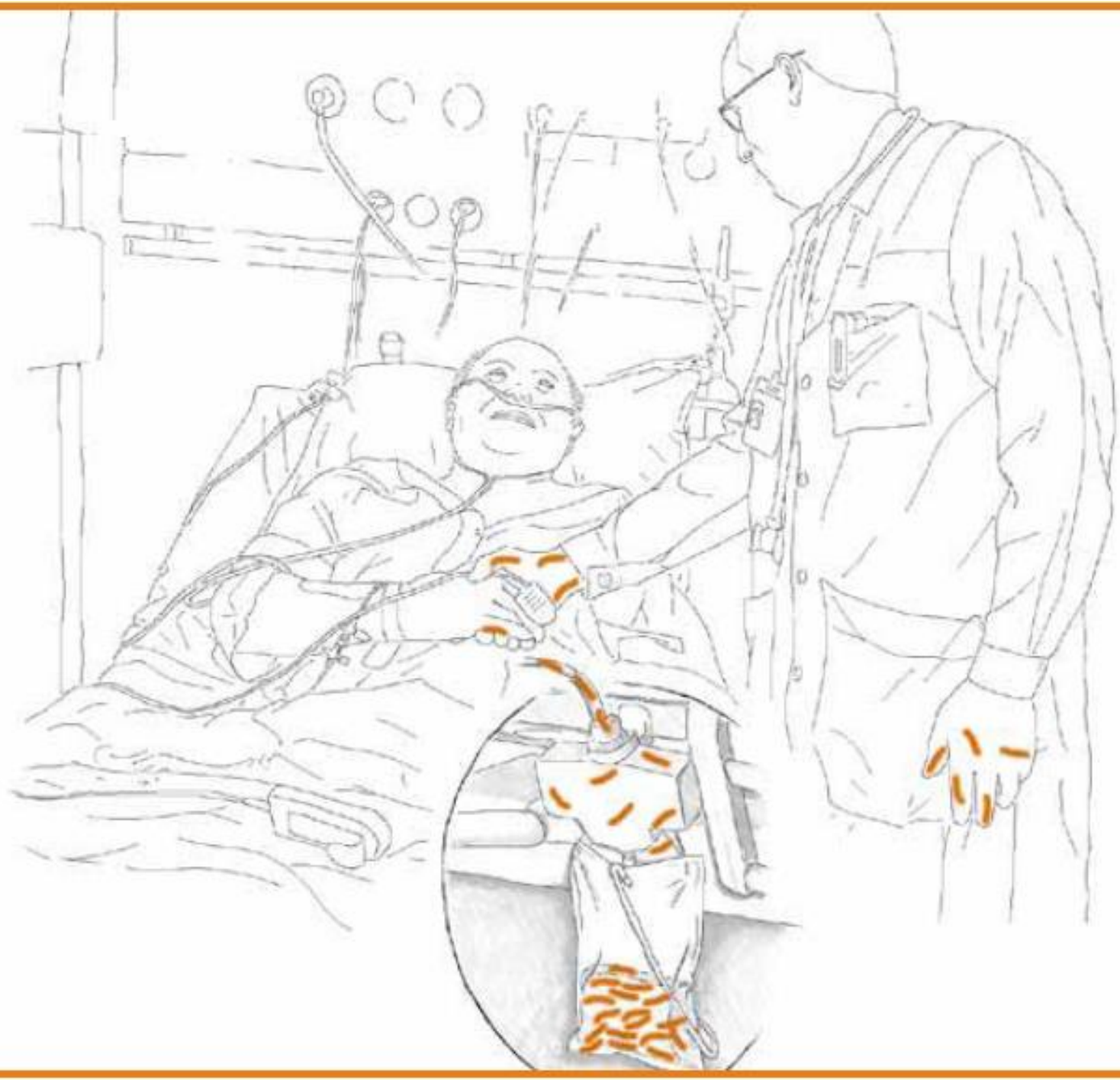


Detection

- Susceptibility testing
  - Breakpoint criteria
    - MIC, zone diameter
- Phenotypic tests
  - The modified Hodge test
  - Biochemical test
  - mass spectrometric detection
- Genotypic identification
  - PCR
  - DNA microarray

Detection

- The identification of *E. coli* or *K. pneumoniae* with overt resistance to **any of the carbapenems** should raise suspicion of **CRE**
- An isolate that is **susceptible to third generation cephalosporins** but **resistant to imipenem** should raise the possibility of
  - Serratia marcescens enzyme (SMC)
    - Serratia species
  - non-metalloenzyme carbapenemase (NMC) or imipenem-hydrolyzing beta-lactamase (IMI)
    - *Enterobacter* species

Detection

- In 2010, the Clinical and Laboratory Standards Institute (CLSI) updated new MIC and disk diffusion breakpoints for the Enterobacteriaceae
  - lower MICbreakpoints, larger zone diameters
  - Up to **87%** of **KPC-producing** *K. pneumoniae* were **reported to be susceptible** to carbapenems according to **breakpoints typically in use prior to 2011**

Interpretive Criteria for Carbapenems and Enterobacteriaceae

Agent	Previous Breakpoints (M100-S19) MIC (µg/mL)			Current Breakpoints (M100-S22) MIC (µg/mL)		
	S	I	R	S	I	R
Doripenem	-	-	-	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty Second Informational Supplement (January 2012). CLSI document M100-S22. Wayne, Pennsylvania, 2012.

Detection

- In clinical laboratories that have implemented **new breakpoints**, **additional tests** to detect extended-spectrum beta-lactamases and carbapenemases **need not be routinely performed** for clinical management.

CRE Definition

The *Previous* CDC definition

- **Nonsusceptible** to imipenem, meropenem, **or** doripenem

  AND

- Resistant to all 3rd gen cephalosporins tested

  - was designed to be more specific for CP-CRE

CRE Surveillance Definition

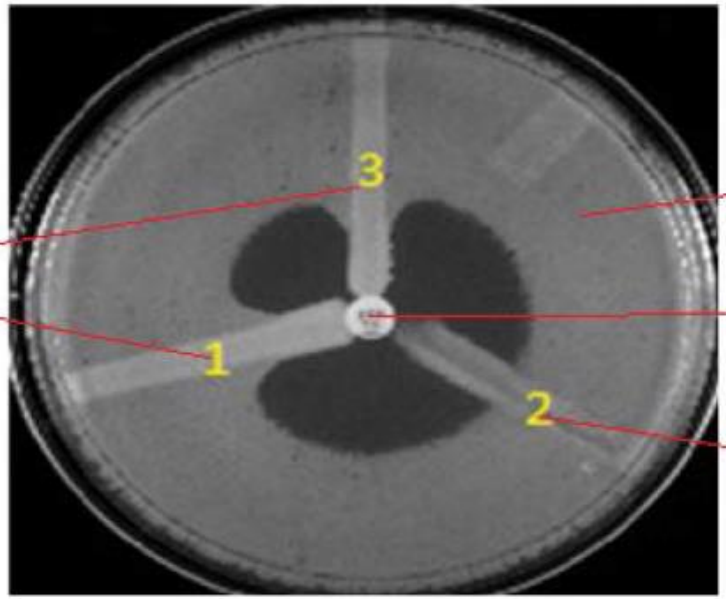
Current CDC Definition (January 2015)

- Resistant to imipenem, meropenem, doripenem, **or** ertapenem

  OR

- documentation that the isolate possess a carbapenemase

Modified Hodge test



Incubated at 37C for 24hrs

Modified Hodge test

- used to detect carbapenemase activity
- poor sensitivity for MBLs detection
  - can be improved with the addition of zinc
  - False negative
- false positive tests have been reported

Clinical Diseases

- Blood stream infections
- ventilator-associated pneumonia
- urinary tract infections
- central venous catheter infections
- Surgical site infections
- etc

Treatment

- Should be tailored to ATB susceptibility results for agents outside the beta-lactam and carbapenem classes
- Additional antibiotic susceptibility testing should be requested for
  - colistin or polymyxin B
  - Tigecycline
  - Fosfomycin
  - Aztreonam

Treatment

- combination ATB therapy with ≥ 2 agents
  - the concern for emergence of resistance during monotherapy
  - the lack of clearly effective single drug
  - Polymyxin plus tigecycline
    - Carbapenem as a third agent?
      - Extended infusion meropenem
    - Plus rifampin?

Infection Control

- Contact precautions
- hand hygiene
- minimizing the use of invasive devices
- antimicrobial stewardship