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- Bacteriology
- Epidemiology
- Molecular biology
- Pharmacology



• Apology



Public Health Abbreviations

- **GNR**
- CRE
- CPE
- **KPC**
- **NDM**
- **PDQ**
- MCQ / SAQ
- UTI

- **WLTM** •
- VIM
- **ESBL**
- **GSOH**
- **OXA-48**
- IMP
- LOL •







Enterobacteriaceae	Non-fermenters	Fastidious organisms
(coliforms)		
Bowel flora	Live in the environment	Awkward to grow
E. coli	Pseudomonas aeruginosa	Campylobacter
Klebsiella	Acinetobacter baumannii	Pertussis
Enterobacter, Serratia, Citrobacter		
Proteus, Providencia, Morganella	Ralstonia	Legionella
Salmonella, Shigella, Yersinia	Burkholderia (cepacia complex, pseudomallei)	Haemophilus, Actinobacillus, Cardiobacterium, Eikinella, Kingella
	Elizabethkingia meningoseptica	
	Stenotrophomonas maltophilia	Franciscella, Pasteurella



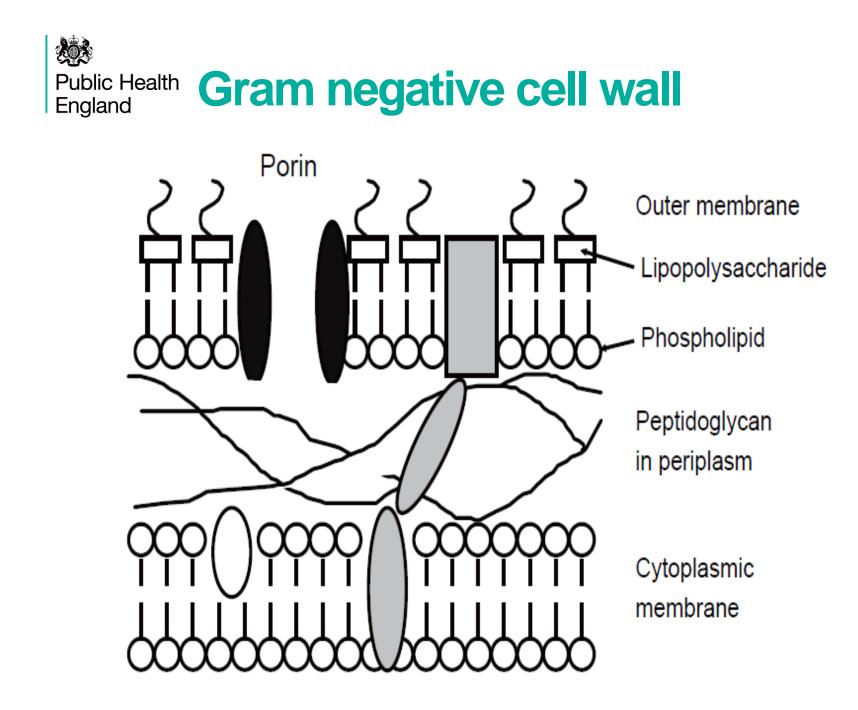
- What infections do they cause?
- How do you treat them?

• What resistance mechanisms are there?



Enterobacteriaciae (coliforms)

- What infections do they cause?
 - bowel flora
 - urinary tract infection (UTI), biliary tract, bowel, occasionally pneumonia
 - bacteraemia
- How do you treat them?
 - remove the catheter, drain the abscess
 - consider antibiotics
- What resistance mechanisms are there?
 - beta-lactams
 - beta-lactamases (ESBL, ampC, OXA (particularly OXA-48), KPC, NDM, VIM)
 - porins, efflux
 - others





- Common
- *E. coli* (community & hospital), *Klebsiella* (hospital)
 - most if not all DGH's in UK affected, GP patients
- Resistant to 3rd generation cephalosporins
 - usually resistant to gentamicin, ciprofloxacin and trimethoprim (≈80%)
 - often amikacin susceptible
- Plasmid borne (readily transmissible)
- Addiction system
- Treatment limited, mortality increased



- Treatment
 - Drain the abscess
 - Remove the catheter
- IV
 - Meropenem, imipenem, doripenem or ertapenem (carbapenem)
 - Temocillin, tigecycline, fosfomycin, colistin, +/- amikacin
 - $-\beta$ -lactam β -lactamase inhibitor
- PO
 - Nitrofurantoin, fosfomycin, pivmecillinam



What happens when you use lots of carbapenems?



- Mechanisms
 - Carbapenemase (enzyme that destroys carbapenems)
 - Porins
 - May have both, along with ESBL and associated coresistance mechanisms

- Names
 - CRE
 - CPE



- KPC
 - K. pneumoniae carbapenemase
- NDM
 - New Delhi metallo-beta-lactamase
- VIM
 - Verona integron-encoded metallo-beta-lactamase
- OXA-48
 - **Oxa**cillinase





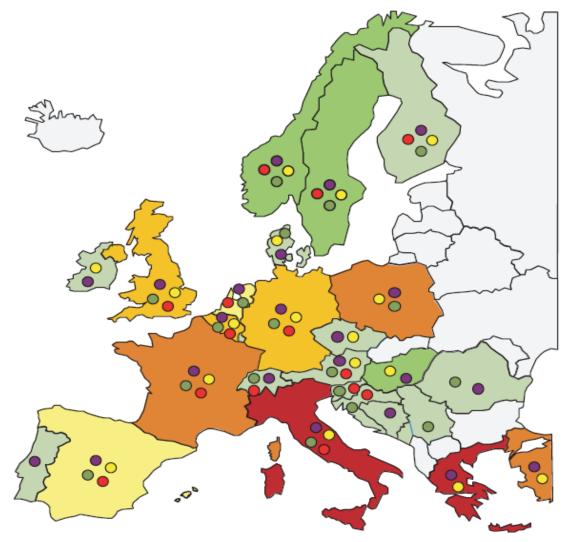


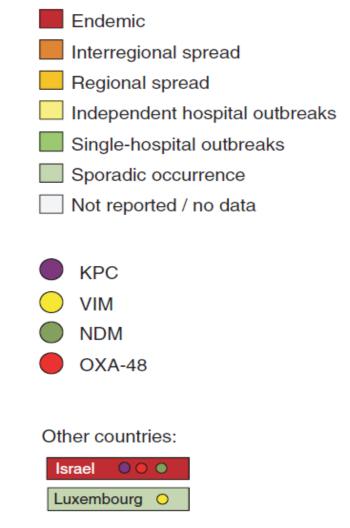












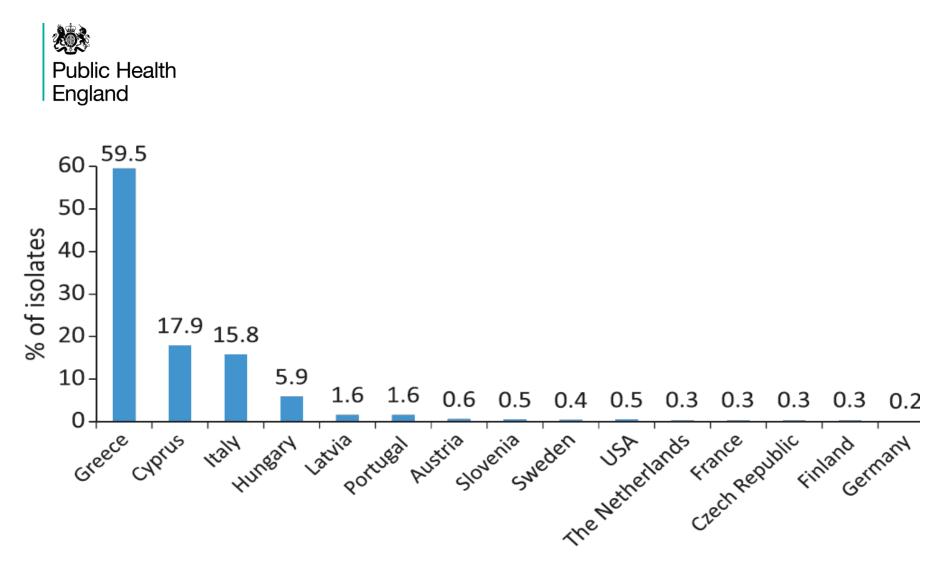


FIG. 2. Rates of non-susceptibility (intermediate plus resistant)



Bangladesh	North Africa (all)		
The Balkans	Malta		
China	Middle East (all)		
Cyprus	Pakistan		
Greece	South East Asia		
India	South/Central America		
Ireland	Turkey		
Israel	Taiwan		
Italy	USA		
Japan			
This is not an exhaustive list; admission to <u>any</u> hospital abroad should be considered when making a risk assessment. Lack of data from a country not included in this list may reflect lack of reporting / detection rather than lack of a carbapenemase problem (which may additionally contribute to an under-estimation of its prevalence)			
UK regions / areas where problems have been noted in some hospitals:			
North West especially:			
Manchester			
London			
IMPORTANT: Healthcare providers have a <u>'duty of care'</u> to proactively communicate any problems they are experiencing with carbapenemase-producing Enterobacteriaceae, <u>not only</u> with colleagues in healthcare settings which are co-terminus, but with any organisation they deal with on the patient pathway, either routinely or sporadically (see Card A.8)			



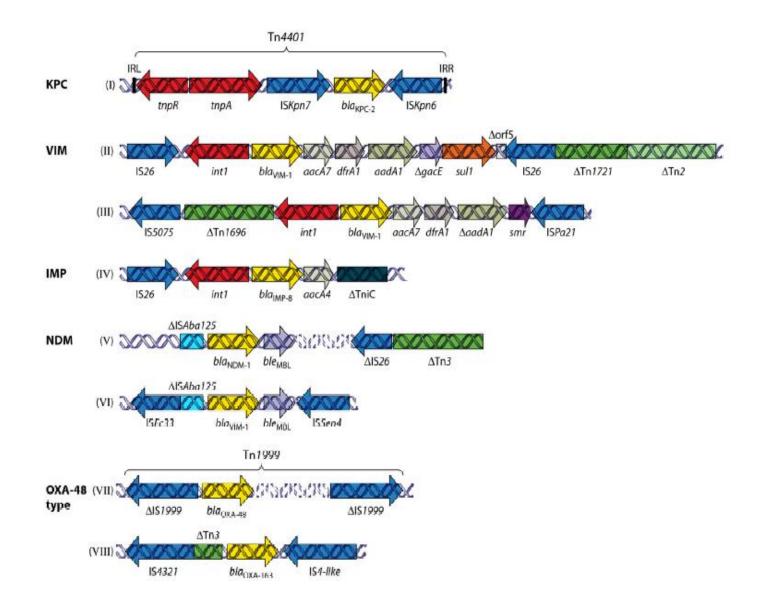




Public Health Carbapenem resistance

×,

England





Public Health Does the resistance mechanism matter?

Yes

- Microbiology
- Epidemiology

Testing •

- OXA can be easily missed in some laboratories
- KPC can also be missed

Transmission? •

– KPC may be more transmissible than NDM / VIM



- <u>Case control study</u>
- 20 cases (KPC **bacteraemia**) and 40 controls
- Mortality was higher for patients with CRE infections compared with those with "CSE" (50.0% versus 25.7%)
- Correa et al 2013
- Suggested reasons
- Effective treatment delayed (awaiting sensitivity testing)
- Available antibiotics are not as good

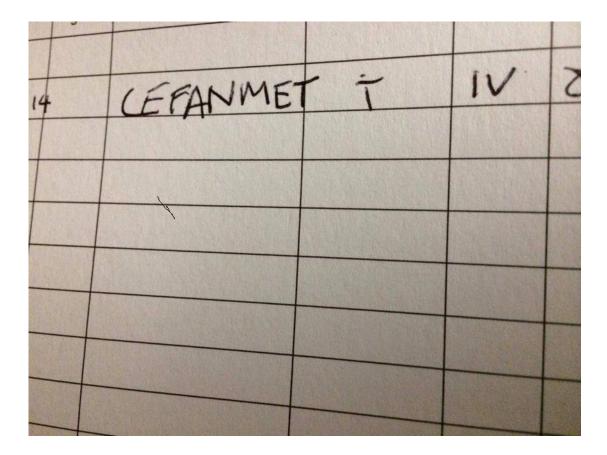
Public Health Who acquires CPE?

- Transplantation (solid organ or stem-cell)
- Mechanical ventilation
- Longer length of stay
- Exposure to antimicrobials:
 - carbapenems, cephalosoprins, fluoroquinolones and vancomycin
- Poor functional status
- Intensive care unit stay





- Colistin
- Fosfomycin ٠
- Tigecycline
- Aminoglycosides ٠ - gentamicin or amikacin
- **Combinations?**
- New agents ٠
 - plazomicin, avibactam





- Nephrotoxicity and neurotoxicity are the principle side effects
- The toxicity demonstrated in earlier studies was almost certainly related to lack of understanding of its PK/PD and the use of inappropriate doses
- Age, high doses, prolonged courses, concomitant vancomycin, hypoalbuminaemia and NSAIDs were independent risk factors for nephrotoxicity
- Monitoring renal function closely is essential for patients receiving colistin
- Other problems
 - Susceptibility testing
 - Dosing (probably need a loading dose; BNF doesn't state this)
 - Dosing is different in cystic fibrosis patients
 - TDM



- Data is limited
- Mainly for UTI
- Some for extra-UTI origin



- Poor mortality data
- IV only
- Bacteriostatic
- Poor bloodstream levels
- Biliary excretion (not useful for UTI)
- Resistance can develop rapidly (whilst receiving therapy)



- Tigecycline plus colistin or gentamicin
- Colistin plus rifampicin
- Colistin plus gentamicin
- Colistin plus meropenem???
 - lower mortality in several studies



Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae







ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients

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Abstract

Healthcare-associated infections due to multidrug-resistant Gram-negative bacteria (MDR-GNB) are a leading cause of morbidity and mortality worldwide. These evidence-based guidelines have been produced after a systematic review of published studies on infection prevention and control interventions aimed at reducing the transmission of MDR-GNB. The recommendations are stratified by type of infection prevention and control intervention and species of MDR-GNB and are presented in the form of 'basic' practices, recommended for all acute care facilities, and 'additional special approaches' to be considered when there is still clinical and/or epidemiological and/or molecular evidence of ongoing transmission, despite the application of the basic measures. The level of evidence for and strength of each recommendation, were defined according to the GRADE approach.

Keywords: Adinetobacter, Burkholderia, Enterobacteriaceae, extended-spectrum β -lactamase, guideline, infection control, multidrug-resistant Gram-negative, outbreak, Pseudomonas, Stenotrophomonas



Guidelines

Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party

A.P.R. Wilson^{a,*}, D.M. Livermore^b, J.A. Otter^c, R.E. Warren^d, P. Jenks^e, D.A. Enoch^f, W. Newsholme^g, B. Oppenheim^h, A. Leanordⁱ, C. McNulty^j, G. Tanner^k, S. Bennett¹, M. Cann^m, J. Bostockⁿ, E. Collins^o, S. Peckitt^P, L. Ritchie^q, C. Fry^r, P. Hawkey^s

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- E. coli
 - -Community
 - Unknown
- Klebsiella spp.
 - -Hospital
 - -Hands
 - -Inappropriate antimicrobial prescribing

Public Health Recommendations – hand hygiene

Epidemic setting

• Strong recommendation: Implement hand hygiene (HH) education programmes (very low level of evidence)

Endemic setting

• Strong recommendation: Implement HH education programmes (moderate level of evidence)



Epidemic setting

- Strong recommendation: Implement contact precautions (CP) for all patients colonized and/or infected with ESBL and CRE (moderate level of evidence)
- Strong recommendation: Use alert code to identify promptly patients already known as colonized with ESBL and CRE at hospital/ward admission and perform screening and pre-emptive CP (moderate level of evidence)
- Strong recommendation: Isolate colonized and infected patients in a single room to reduce the risk of acquisition of ESBL and CRE (moderate level of evidence)
- Strong recommendation: Cohort staff to reduce the risk of acquisition of CRE (moderate level of evidence)

Endemic setting

• Strong recommendation: Implement CP for all patients colonized with ESBL and CRE (moderate level of evidence)



Epidemic setting

- Strong recommendation: Implement a programme of active screening culture at hospital admission followed by contact precautions to reduce the spread of ESBL and CRE
- Endemic setting
- Not recommended
- How do you do it?
- Rectal swab, with "visible material" on the swab



Environmental cleaning

Epidemic setting

- Strong recommendation: Monitor cleaning performance to ensure consistent environmental cleaning (EC)
- Vacate units for intensive cleaning
- Implement regular EC procedures and, when available, dedicate non-critical medical items for use on individual patients with ESBL (moderate level of evidence)
- Endemic setting
- As above

Public Health Antimicrobial stewardship

Epidemic setting

- Strong recommendation: Implement an antimicrobial stewardship programme
- Plan interventions of restriction of antibiotic usage to reduce the spread of ESBL (moderate level of evidence)
- Endemic setting
- As above



- Not mentioned in the guidelines
- Universal bathing on ITU works for MRSA (Huang et al 2013)
- Universal bathing may work for S. aureus and VRE (Climo et al 2013)



Bundle approach (Israel)

- In March 2007, the Ministry of Health issued guidelines mandating physical separation of hospitalized carriers of carbapenem-resistant Enterobacteriaceae (CRE) and dedicated staffing and appointed a professional task force charged with containment
- The task force paid site visits at acute-care hospitals, evaluated infection-control policies and laboratory methods, supervised adherence to the guidelines via daily census reports on carriers and their conditions of isolation, provided daily feedback on performance to hospital directors, and intervened additionally when necessary
- By 31 March 2007, 1275 patients were affected in 27 hospitals (175 cases per 1 million population). Prior to the intervention, the monthly incidence of nosocomial CRE was 55.5 cases per 100,000 patient-days. With the intervention, the continuous increase in the incidence of CRE acquisition was halted, and by May 2008, the number of new monthly cases was reduced to 11.7 cases per 100,000 patient-days (P<.001)
- There was a direct correlation between compliance with isolation guidelines and success in containment of transmission (P=.02). Compliance neutralized the effect of carrier prevalence on new incidence (P=.03).
- A centrally coordinated intervention succeeded in containing a nationwide CRE outbreak after local measures failed



Bundle approach

- Screen patients for KPC on admission and then fortnightly
- Contact isolation and geographic separation
- Bathing all patients daily with chlorhexidine
- HCW education
- Adherence monitoring
- (Hayden et al 2015)

- Daily 2% chlorhexidine gluconate baths for patients
- Enhanced environmental cleaning
- Surveillance cultures at admission
- Serial point prevalence surveillance (PPS)
- Isolation precautions
- Training of personnel
- (Munoz-Price et al 2010)





- <u>CRE</u>
- Oral gentamicin, 80 mg QDS was administered to 50 consecutive patients with gut colonization by gentamicin-susceptible CRE in cases of **planned surgery**
- The overall decontamination rate was 68% (34/50)
- In the six-month period of follow-up:
 - CRE infections were documented in 5/34 (15%) successfully decontaminated patients compared to 12/16 (73%) persistent carriers (P<0.001)
 - The decontamination rate was 96% (22/23) in patients receiving oral gentamicin only, compared to 44% (12/27) of those treated with
 oral gentamicin and concomitant systemic antibiotic therapy (CSAT) (P<0.001)
 - In the follow-up period, CRE infections were documented in 2/23 (9%) of patients treated with oral gentamicin only and in 15/27 (56%) of those also receiving CSAT (P=0.003)
 - No difference in overall death rate between different groups was documented
 - The risk of emergence of gentamicin-resistant CRE should be considered



- ESBL
- Double blind RCT
- Oral gentamicin and colistin versus placebo
- Temporary reduction in ESBL carriage
- No long-term benefit



- Consecutive hospitalized CRE carriers were studied. Patients whose rectal isolates were gentamicin sensitive but colistin resistant were treated with gentamicin. Patients whose isolates were colistin sensitive but gentamicin resistant were treated with colistin. Patients whose isolates were sensitive to both drugs were randomized to 3 groups of oral antibiotic treatment: gentamicin, colistin, or both. Patients whose isolates were resistant to both drugs, and those who did not consent, were followed for spontaneous eradication.
- 152 patients were included
 - 102 were followed for spontaneous eradication for a median duration of 140 days (controls)
 - 50 received 1 of the 3 drug regimens: gentamicin, 26; colistin, 16; both drugs, 8, followed for a median duration of 33 days
- Eradication rates in the 3 treatment groups were 42%, 50%, and 37.5%, respectively
- Each significantly higher than the 7% spontaneous eradication rate in the control group (P < .001, P < .001, and P = .004, respectively) with no difference between the regimens
- No significant adverse effects were observed
- Conclusion
- Oral antibiotic treatment with nonabsorbable drugs to which CRE is susceptible appears to be an effective and safe for eradication of CRE colonization



- 14 consecutive patients (16%) were treated with a short course (7 days) of selective digestive decontamination (SDD), employing colistin (1 million units q.i.d.) and gentamicin (80 mg q.i.d.) as oral solutions, and applying colistin/gentamicin gel (0.5 g) to the oral cavity
- In a retrospective analysis, these 14 SDD patients were compared with the remaining 76 patients harbouring KPC-2-KP. KPC-2-KP carrier status was followed in all 14 SDD patients by submitting stool samples to KPCspecific PCR
- The mean follow-up period was 48 days (range 12–103 days). Successful elimination of KPC-2-KP was defined as a minimum of three consecutive negative PCR test results separated by ≥48 h each
- Decolonisation of KPC-2-KP was achieved in 6/14 patients (43%) after a mean of 21 days (range 12–40 days), but was also observed in 23/76 (30%) of the non-SDD controls (P = 0.102)
- SDD treatment resulted in the development of secondary resistance to colistin (19% increase in resistance rate) and gentamicin (45% increase) in post-treatment isolates
- In the control group, no secondary resistance occurred
- We conclude that the SDD protocol applied in this study was not sufficiently effective for decolonisation and was associated with resistance development.



Faecal transplantation

- We report a case in which faecal microbiota transplantation (FMT) utilized for relapsing *Clostridium difficile* colitis successfully eradicated colonization with several multidrug-resistant organisms (MDROs)
- FMT may have an additive benefit of reducing MDRO carriage and should be further investigated as a potential measure to eradicate additional potentially virulent organisms beyond *C. difficile*



Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae







- One or two problems with it...
- CPE are an emergent and real threat
- Board involvement
 - allocation of resources
- Hopefully *prevent* what happened with MRSA / C. difficile
- Manchester
 - real problems...
 - not "going away" (unlike MRSA, C. difficile)*
 - as for Greece, Italy, certain parts of the USA...

A.2 Early recognition of individuals who mayEnglandbe colonised / have an infection

- Assess <u>each patient</u> on admission, readmission OR on transfer from another healthcare facility IN THE LAST 12 MONTHS HAS THE PATIENT:
- Been an inpatient in a hospital abroad
 - OR
- Been an inpatient in a UK hospital known to have had problems with spread of CRE
 - OR
- Previously been colonised or had an infection with CRE or close contact with a person who has, if known
- If one or more of above applies then:
- The patient is considered to meet the criteria for being a suspected case of CRE colonisation or infection (as applicable) AND REQUIRES IMMEDIATE ISOLATION PLUS
 - instigation of *strict standard precautions* to prevent possible spread
 - screening to assess current status for colonisation or infection
 - assessment for appropriate treatment

Public Health England A.3 Early isolation of suspected and laboratory-confirmed cases

- If the patient already has laboratory-confirmed infection or colonisation with CRE *OR* meets the criteria for a suspected case then:
- Advise the patient (and relatives if appropriate) of the positive result or your suspicions (whichever applies) and your management plan – provide patient information leaflet
 - -AND
- Immediately place the patient into a single room with en suite facilities and send screening samples
 - AND
- Apply strict standard precautions in all settings



A.3 Early isolation of suspected and laboratory-confirmed cases

- All suspected (including previously positive) patients should be isolated until screening results are known. If the patient is **POSITIVE** on screening for CRE or is a laboratory-confirmed case (colonisation or infection):
 - they should remain in isolation for the duration of their hospital stay
 - the hospital CRE Management Plan should be revisited
 - comprehensive awareness raising of the plan should take place amongst staff including doctors, nurses, physiotherapists, domestics and others with patient contact
- Strict standard precautions must be practiced (whether the patient has infection or colonisation) including:
 - good hand hygiene
 - where any part of a staff uniform, not protected by an ordinary apron, is expected to come into contact with the
 patient, a long-sleeved disposable gown should be used
 - use of personal protective equipment (PPE) in line with standard precautions
 - environmental cleaning and decontamination, with an enhanced focus on frequent cleaning of hand contact areas
- If **NEGATIVE** a further two negative samples need to be achieved and a risk assessment undertaken before removing from isolation (48h apart)



th A.4 Early detection – screening of suspected cases and contacts

- SCREEN THE PATIENT:
 - Immediately arrange for the patient to be screened provide explanation & factsheet
- AND
 - Ensure that the necessary laboratory personnel and health professionals have been informed
- WHAT SAMPLES TO TAKE:
 - Take a rectal swab (visible faecal material on the swab) OR a stool sample
- AND
 - Send to laboratory as soon as possible marking request form: <u>'Possible CRE</u>
 <u>'colonisation or infection'</u> (or 'exposure' if a contact)
- ALSO
 - If patient is known to have been hospitalised in the last 12 months in a country with reported high prevalence (or area known to have a CRE problem), include samples from any wounds and device-related sites



Public Health A.4 Early detection – screening of suspected cases and contacts

- SCREENING OF CONTACTS:
- Provide contact leaflet and undertake screening for contacts of a positive case based on the likelihood of exposure as follows:
 - Screening of patients in the same setting is NOT normally required if the case was identified on admission and isolated immediately
 - Screening of patient contacts of a positive case SHOULD be undertaken if the case had spent time (or remained) in an open ward or bay with other patients before (or despite) having a positive result for CRE
 - –3. Screening of household contacts and healthcare staff is NOT required

A.4 Early detection – screening of suspected cases and contacts

- If NEGATIVE on screening the patient should remain in isolation until a further two consecutive samples test negative samples being taken 48 hours apart i.e. day 0 (the initial sample), day 2 and day 4 (the further samples)
- Once achieved they can be removed from isolation with no further screening required

A.4 Early detection – screening of suspected cases and contacts

• If **POSITIVE** (either from a screening sample OR from a routine clinical sample from this admission episode) the patient should remain in isolation, preferably for the duration of their hospital stay



ADDRESSING CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE – RISK PRIORITISATION OF INFECTION PREVENTION AND CONTROL (IP&C) MEASURES, SCREENING AND ISOLATION – ROLL-OUT PLAN (see note, page 2).

For use in conjunction with the Acute trust toolkit for the early detection, management and control of carbapenemase–producing Enterobacteriaceae¹

		Known or recently confirmed case of carbapenemase- producing Enterobacteriaceae ²	Direct medical transfer from or specialist / augmented care ³ in last 12 months in country or UK care setting with <i>known</i> <i>high prevalence</i> ¹	Medical tourist ⁴ from country with known high prevalence ¹	History of hospitalisation in last 12 months in country or UK care setting with known high prevalence ¹	Identified as contact of positive case (colonisation or infection)	Medical transfer from / history of hospitalisation in last 12 months in country with no reported problems	No risk factors identified on admission
THE CARE ENVIRONMENT		HIGH		MEDIUM		LOW		
Admission to or receiving care in specialist / augmented care unit ³	HIGH							
Admission to or receiving care in acute general ward	MEDIUM							
Day care	MEC	**	**	**	**	**		N/A
Outpatient clinic	MOT	**	**	**			N/A	N/A



	Isolate immediately in a side room with en suite facilities (or dec	dicated commode) and retain in isolation as follows:					
High risk	 Suspected case – isolate until 3 consecutive NEGATIVE screens (if still in hospital). Should any sample screen positive treat as a confirmed case Known case or case confirmed via clinical / screening sample (further screening not required) – isolate throughout hospital stay 						
	Known case or case confirmed via clinical / screening sa	ample (lurther screening not required) – <i>isolate throughout nospital stay</i>					
	Isolate in side room with en suite facilities (or dedicated commode) if possible (see increased transmission risks) until first screening result demonstrates NEGATIVE. If not possible to continue isolation (in line with toolkit ¹) then:						
	EITHER cohort patient in line with toolkit ¹ and in discussion with your IP&C team						
	OR, if not possible to cohort, nurse with strict emphasis on maintaining compliance with standard precautions and optimal environmental cleaning (without fail)						
isk	AND submit further 2 samples to achieve 3 consecutive NEGATIVE screens if still in hospital. Should any sample test positive treat as a confirmed case.						
	**For outpatients and day cases (note: this is supplementary advice to that provided in the toolkit to assist risk assessment): provide appointment timed for end of clinic or list; consider caring for day case in single room depending on facilities and on degree of contact with body fluids (see below: increased transmission risks). Maintain compliance with standard precautions and optimal environmental cleaning (without fail).						
Low risk	No action, other than be alert to change in risk-level in light of any further information relating to patient status. Maintain compliance with standard precautions and optimal environmental cleaning (without fail).						
Increased patients w		sion risk should be taken into account when prioritising side rooms, they are					
	arrhoea	Medical devices in situ					
	continence (urine or faeces)	 Ventilatory support requirements 					
• Dis	scharging wounds high risk of wandering and unable to comply with good hygiepic	Additionally, consider:					
 Dis A I 	high risk of wandering and unable to comply with good hygienic actices	 Additionally, consider: Risks posed from inadequate decontamination of equipment where there is high contact with body fluids e.g. endoscopes 					
Dis A I pra	high risk of wandering and unable to comply with good hygienic actices nis matrix is intended to inform preparation of a roll-out plan. The g	 Risks posed from inadequate decontamination of equipment where there is high contact with body fluids e.g. endoscopes gold standard for any patient admitted who is a suspected case of carbapenemase 					
Dis A I pra NOTE: Th producing	high risk of wandering and unable to comply with good hygienic actices nis matrix is intended to inform preparation of a roll-out plan. The g	 Risks posed from inadequate decontamination of equipment where there is high contact with body fluids e.g. endoscopes gold standard for any patient admitted who is a suspected case of carbapenemase ediately and manage in line with the <i>Acute trust toolkit</i>¹. However, where risk 					



- *Who* does the risk assessment on admission?
- When does the risk assessment take place?
- *How* do you educate all front line staff?
- The CRE situation is fluid / evolving. Which are the high risk hospitals? Where in the UK is "high risk?"
- How do you prioritise side rooms (with en-suite facilities)?
 - Symptomatic C. difficile, MRSA in a sputum, dying patients
- Consent issues
- How does your laboratory screen?
- Patient admitted with CRE isolated for duration of hospital stay
 - Patient re-admitted screen and potentially only isolate for 96h



- Haemodialysis patient travels to India
- What do you currently do on their return?
- What do you think you should do on their return?
- By the way...
 - One side room
 - Another patient on the unit with MDR TB (not coughing) and another with MRSA in a sputum sample



- Renal transplant recipient transferred from Leeds for rehabilitation post CVA
- What do you currently do on their return?
- What do you think you should do on their return?
- By the way...
 - One side room
 - Another patient on the unit with C. difficile (toxin positive) and loose stools



- Serious threat
- Vulnerable patients
- Associated with significant *increased* mortality and morbidity
- Very difficult to treat
- Very difficult to control
- Very difficult to study so as to find out more information
- Initially hospital patients these will be discharged home / to nursing / residential home +- district nurse care
- We can do something and we must do something!



- Acknowledgements
- Apologies
- Questions