Hull and East Yorkshire Hospitals NHS Trust

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Clinical presentations and impact of (resistant) GNB infections in the UK

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Is resistance in GNB impacting the incidence of GNB infection in the UK?

J Antimicrob Chemother 2012; **67**: 1514–1524
doi:10.1093/jac/dks082 Advance Access publication 9 March 2012

Journal of Antimicrobial Chemotherapy

Increasing incidence of *Escherichia coli* bacteraemia is driven by an increase in antibiotic-resistant isolates: electronic database study in Oxfordshire 1999–2011

Iryna Schlackow[1], Nicole Stoesser[1,2], A. Sarah Walker[1,3], Derrick W. Crook[1], Tim E. A. Peto[1] and David H. Wyllie[1,4]* on behalf of the Infections in Oxfordshire Research Database (IORD) Team†

Severity of infection and mortality (17%; N=2080) were not impacted by resistance

Is resistance in GNB influencing process/quality of care?

Increasing consumption of the *last resort* antibiotics

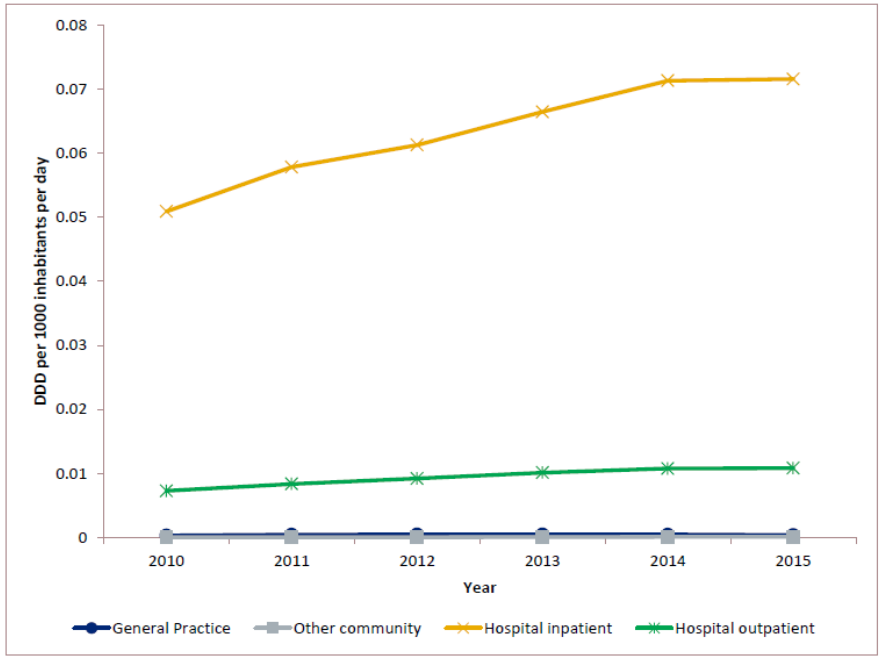
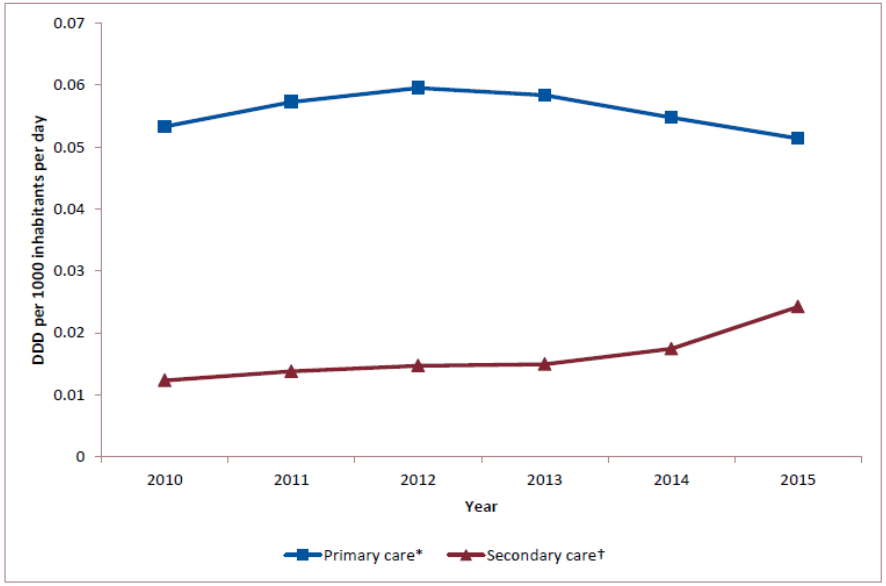


Figure 3.7 Consumption of carbapenems, by prescriber location, expressed as DDD per 1000 inhabitants per day, England, 2010-2015



* Includes general Practice, Dentist and other community prescribing

† Includes inpatient and outpatient prescribing

Figure 3.19 Consumption of colistin in primary and secondary care, England 2010 - 2015

ESPAUR Report 2016

Is resistance in GNB influencing process/quality of care?

ORIGINAL ARTICLE BACTERIOLOGY

Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals

J. M. Fitzpatrick[1], J. S. Biswas[2], J. D. Edgeworth[2], J. Islam[3], N. Jenkins[4], R. Judge[5], A. J. Lavery[6], M. Melzer[7], S. Morris-Jones[6], E. F. Nsutebu[8], J. Peters[1], D. G. Pillay[4], F. Pink[7], J. R. Price[9], M. Scarborough[10], G. E. Thwaites[11], R. Tilley[5], A. S. Walker[10,11] and M. J. Llewelyn[1,12], on behalf of the United Kingdom Clinical Infection Research Group

- 17% (N = 616) received initial antibiotic therapy that was not active in-vitro
- Resistance to co-amoxiclav = 36% (most commonly used antibiotic [32%])
- Using dual therapy (usually aminoglycoside) decreased likelihood of in-vitro inactivity
  - 27% to 2% for co-amoxiclav
  - 15% to 6% for piperacillin/tazobactam
- Inappropriate therapy, however, not associated with outcome

Is GNB resistance in UK influencing patient outcomes?

Journal of Antimicrobial Chemotherapy (2006) **58**, 1000–1008
doi:10.1093/jac/dkl368
Advance Access publication 23 September 2006

JAC

Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care

C. A. M. McNulty[1]*, J. Richards[2], D. M. Livermore[3], P. Little[4], A. Charlett[3], E. Freeman[5], I. Harvey[6] and M. Thomas[7,8]

Patients with resistant isolates had:

- Longer time to symptom resolution (7 vs 4 days, P = 0.0002)
- More re-consultations (39% vs 6% in first week, P <0.0001)
- More subsequent antibiotics (36% vs 4% in first week, P <0.0001)

ORIGINAL ARTICLE BACTERIOLOGY

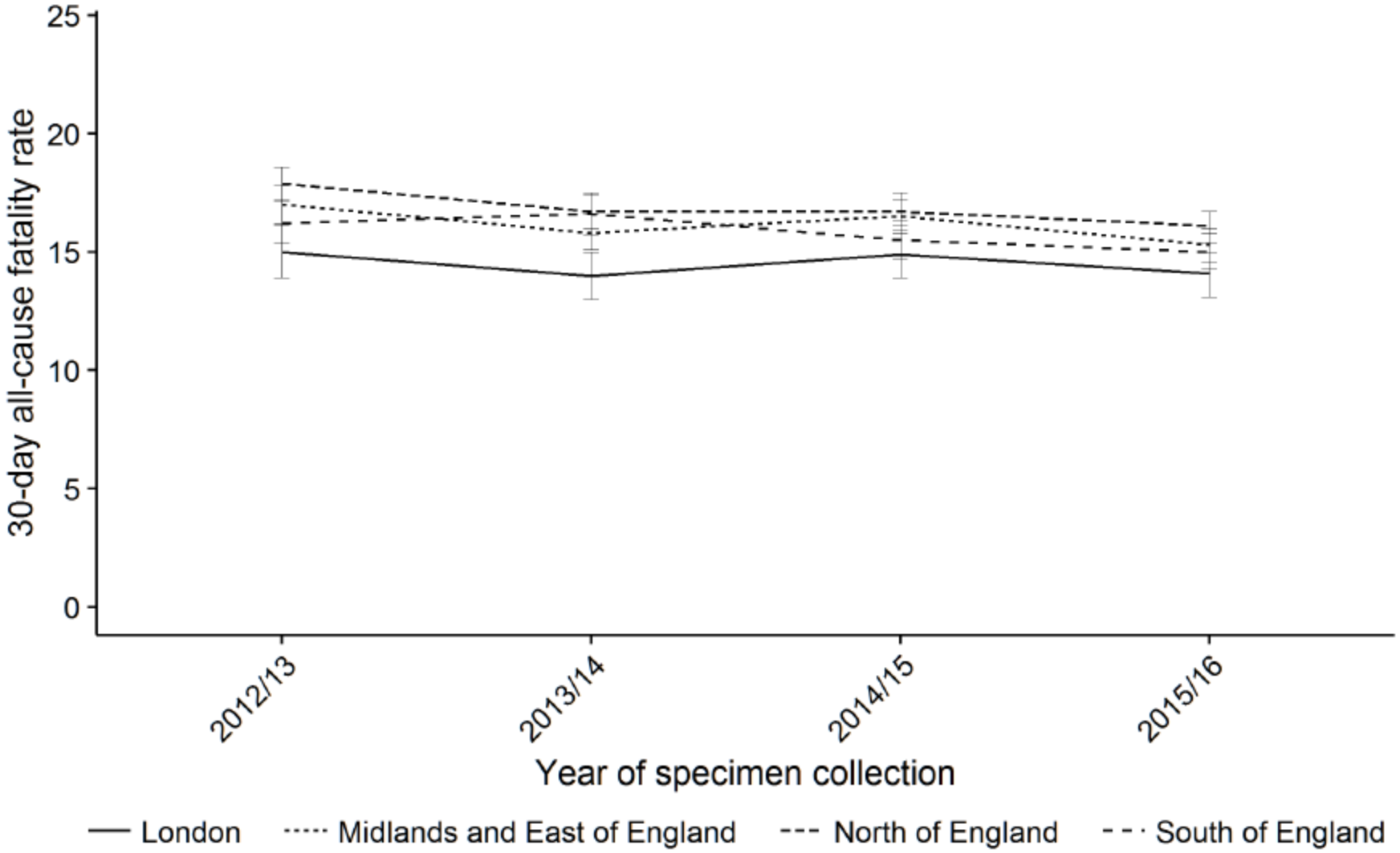
Thirty day all-cause mortality in patients with *Escherichia coli* bacteraemia in England

J. K. Abernethy, A. P. Johnson, R. Guy, N. Hinton, E. A. Sheridan and R. J. Hope

Healthcare Associated Infection and Antimicrobial Resistance Department, Public Health England, Colindale, London, UK

		Crude and adjusted odds ratios of risk factors associated with 30-day all-cause mortality					
Factor		Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Cephalosporin susceptibility[b]	S	1			1		
	NS	1.28	(1.14–1.44)	<0.0001	1.08	(0.93–1.26)	0.303
Carbapenem susceptibility[b]	S	1					
	NS	1.51	(0.60–3.80)	0.62	Not included		
Ciprofloxacin susceptibility[b]	S	1			1		
	NS	1.37	(1.25–1.50)	<0.0001	1.30	(1.15–1.46)	<0.0001

Figure 7. Thirty-day all-cause case fatality rate by NHS Region following *E. coli* bacteraemia



Is resistance in GNB influencing the cost of care?

OPEN ACCESS Freely available online

PLoS MEDICINE

Mortality and Hospital Stay Associated with Resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe

Marlieke E. A. de Kraker[1,2]*, Peter G. Davey[3], Hajo Grundmann[1,2], on behalf of the BURDEN study group

For third generation cephalosporin-resistant E. coli, UK in 2007:

- Excess bed days 22,300
- Excess costs £5,147,000
- Excess mortality 504

Case 1

- 33 years
- Bilateral hip replacements in Nigeria 2011
- L hip required “washout” after primary operation, but ongoing pain such that unable to walk; wound healthy
- Underwent 1st stage revision in UK, April 2015; no pre-operative microbiology
- Gentamicin spacer inserted

Case 1

- Pre-operative ID consult:

Start IV Teicoplanin/Meropenem immediately post-sampling.
The Meropenem is because he is from Nigeria i.e. ESBL producer

ESBL-producing *Enterobacter cloacae*

Antibiotic	Hip tissue (multi)
Amikacin	**S**
Aztreonam	R
Cefotaxime	R
Ciprofloxacin	R
Chloramphenicol	R
Co-amoxiclav	R
Colistin	**S**
Co-trimoxazole	R
Ertapenem	**S**
Fosfomycin	**S**
Gentamicin/Tobramycin	R
Meropenem	**S**
Piperacillin-tazobactam	R
Temocillin	**S**
Tigecycline	**S**

Case 1

ESBL-producing *Enterobacter cloacae*

- Meropenem 2g/6h for 6/52
- Wound leak within a few days of stopping
- Debridement, removal of spacer, further sampling and VAC dressing

ESBL-producing *Enterobacter cloacae* (again!)

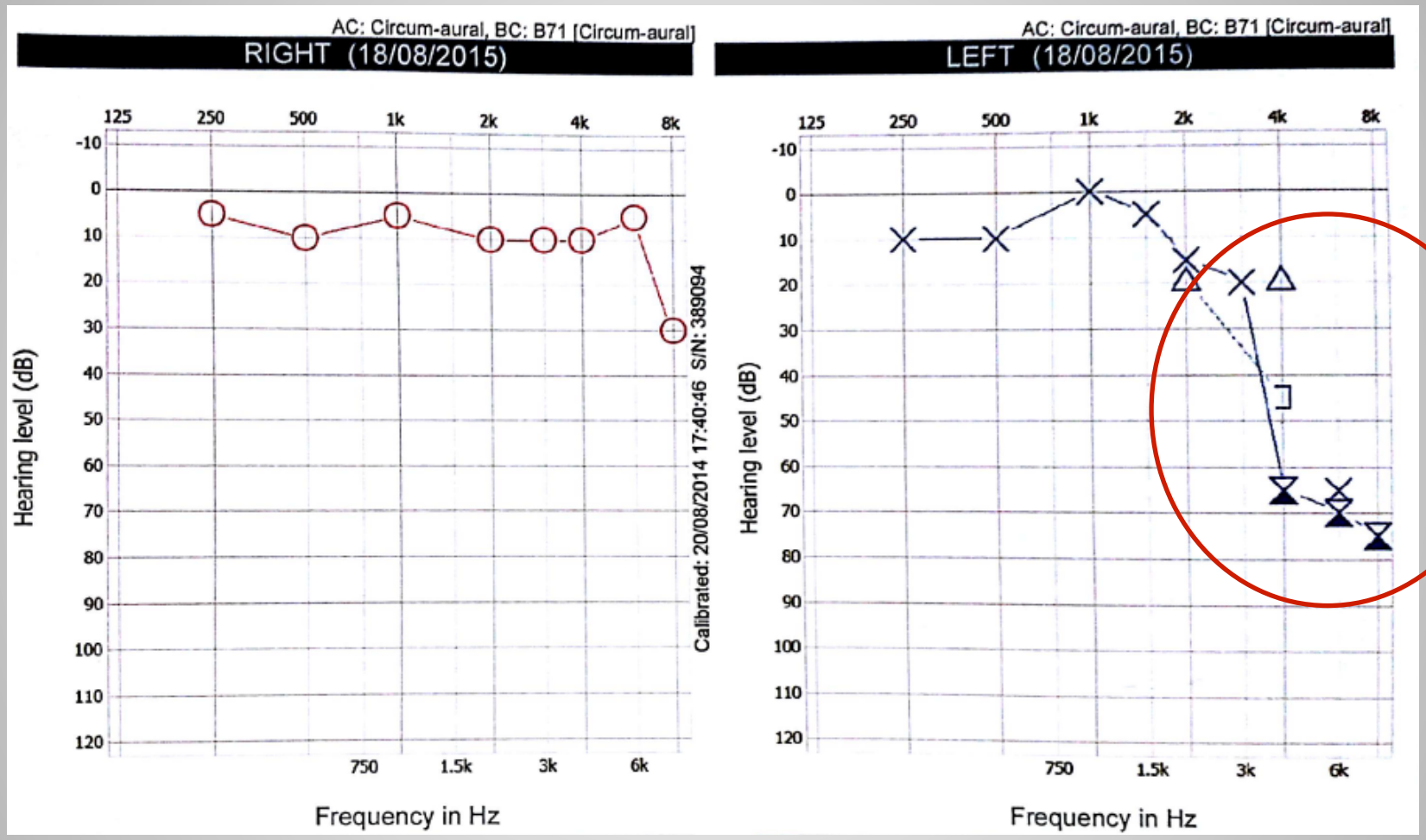
Antibiotic	Hip tissue (multi)
Amikacin	**S**
Aztreonam	R
Cefotaxime	R
Ciprofloxacin	R
Chloramphenicol	R
Co-amoxiclav	R
Colistin	**S**
Co-trimoxazole	R
Ertapenem	**S**
Fosfomycin	**S**
Gentamicin/Tobramycin	R
Meropenem	**S**
Piperacillin-tazobactam	R
Temocillin	**S**
Tigecycline	**S**

Case 1

ESBL-producing *Enterobacter cloacae*

- Meropenem 2g/8h 12/52 *plus* Amikacin with weekly therapeutic drug monitoring; trough level always <1.5
- Two further planned debridements then wound closed; no further + microbiology
- Complained of buzzing/hearing loss left @ week 11

Audiology



- Subsequently successfully underwent 2nd stage
- All 2nd stage samples negative

Case 1

Impact of resistance

- Use of prolonged broad-spectrum IV agents
- No oral options
- More operations than usual
- Prolonged hospital stay
- Therapeutic drug monitoring of amikacin
- Hearing loss L ear

Case 2

- 83 years
- Out of hospital cardiac arrest in Tenerife
- *Successfully* resuscitated
- Admitted to ICU in Spain; thoracotomy and plating and wiring of # ribs; bilateral chest drains
- Repatriated back to UK!
- Received imipenem/cilastin in Spain, but stopped on repatriation

Non-metallo-carbapenemase producing *Acinetobacter baumannii*

(OXA 51/58 +; international clone type 2)

Antibiotic	Respiratory specimens (multi)
Amikacin	**S**
Ceftazidime	R
Ciprofloxacin	R
Colistin	**S**
Co-trimoxazole	R
Tobramycin	**S**
Meropenem	R
Piperacillin-tazobactam	R
Tigecycline	R

Also Pseudomonas in respiratory specimens; fully sensitive

Case 2

- No antibiotics initially, but patient deteriorated with some collapse/consolidation left lower lobe
- Previous UK study suggested low attributable mortality; low impact of therapy on outcome

[Antimicrobial treatment and clinical outcome for infections with carbapenem- and multiply-resistant *Acinetobacter baumannii* **IJAA** (2008)]

- Treated with high-dose IV Meropenem plus nebulised Tobramycin 14/7
- Clinically improved

Case 2

Impact of resistance

- Infection control implications
- Use of broad-spectrum agents
- Knowing when to cover colonising resistant organisms is tricky!

Case 3

- 66 years; previously well
- Emergency excision of malignant small bowel mesenteric tumour (uncontrollable malaena)
- Admitted ICU post-operatively; CV line; commenced TPN
- **Day 9:** Fever; CRP 298 (up++); leucopenia (1.2)
- Blood cultures from CV line, arterial line and peripheral line + GNB (CV<arterial<peripheral)

Case 3

ESBL producing *E.coli*

Antibiotic	All blood cultures (day 0)
Aztreonam	R
Cefotaxime	R
Ciprofloxacin	R
Chloramphenicol	R
Co-amoxiclav	R
Co-trimoxazole	R
Gentamicin	**S**
Meropenem	**S**
Piperacillin-tazobactam	R
Temocillin	**S**

Case 3

- Empiric IV Amoxicillin, Gentamicin, Metronidazole
- Switched to IV Temocillin/Gentamicin and then rationalised to Temocillin monotherapy as “improving”
- Urine, CTAP – NAD
- **Day 15 (day 6 therapy):** CRP 217; WCC 15 (Neutrophilia); peripheral blood culture GNB!
- But hark the CV line had not been removed!

Case 3

ESBL producing *E.coli*

Antibiotic	Blood cultures (day 6 of therapy)
Aztreonam	R
Cefotaxime	R
Ciprofloxacin	R
Chloramphenicol	R
Co-amoxiclav	R
Co-trimoxazole	R
Gentamicin	**S**
Meropenem	**S**
Piperacillin-tazobactam	R
Temocillin	**R**

- CV line removed!
- Meropenem commenced!
- Repeat blood cultures at 48 hours negative

Case 3

Impact of resistance

- Eventual use of broad-spectrum agent (probably could have been avoided)
- Case highlights the potential of the emergence of resistance on therapy/therapy failure if basics are not done well

Case 4

- 78 year old of Nigerian origin
- **29/11/16:** Revision left knee replacement (instability)
- **12/12/16:** Admitted with rigors and documented fever

Case 4

ESBL producing *E. coli*

Antibiotic	Blood	Urine
Amikacin	R	R
Aztreonam	R	R
Cefotaxime	R	R
Ciprofloxacin	R	R
Chloramphenicol	**S**	**S**
Co-amoxiclav	R	R
Co-trimoxazole	R	R
Ertapenem	**S**	**S**
Fosfomycin	**S**	**S**
Gentamicin	R	R
Meropenem	**S**	**S**
Piperacillin-tazobactam	R	R
Tigecycline	**S**	**S**

Case 4

- Empiric IV Co-amoxiclav then Aztreonam and subsequently Meropenem 7/7
- Some discussion about length of therapy
- **23/12/16:** Discharged well
- **10/01/17:** Readmitted with left knee pain/swelling and high CRP
- Had DAIR – turbid fluid at surgery

Case 4

ESBL producing *E. coli*

Antibiotic	Knee tissue (multi)	Prior urine
Amikacin	R	R
Aztreonam	R	R
Cefotaxime	R	R
Ciprofloxacin	R	R
Chloramphenicol	**S**	**S**
Co-amoxiclav	R	R
Co-trimoxazole	R	R
Ertapenem	**S**	**S**
Fosfomycin	**S**	**S**
Gentamicin	R	R
Meropenem	**S**	**S**
Piperacillin-tazobactam	R	R
Tigecycline	**S**	**S**

Case 4

ESBL producing *E. coli*

- Commenced on IV Meropenem 2g/8h *plus* IV Fosfomycin 4g/6h; Meropenem subsequently streamlined to Ertapenem 1g/24h
- **Management:** 8 weeks IV then ongoing oral Chloramphenicol
- Has done surprisingly well: walking with frame; CRP now 0.9 (from 279)

Case 4

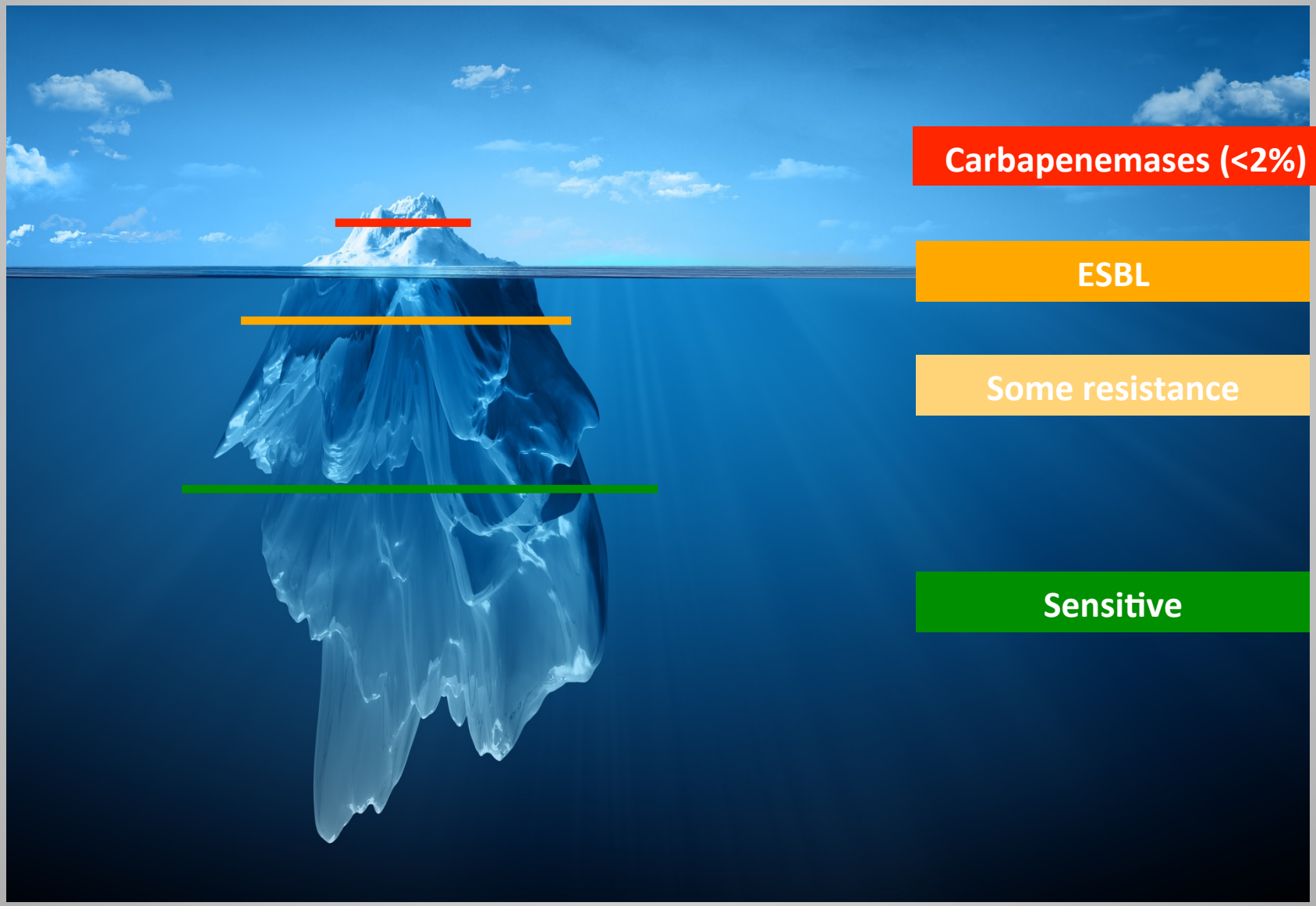
Impact of resistance

- Inappropriate empiric therapy of BSI/UTI
- Use of broad-spectrum agents
- Use of less familiar, expensive antibiotics
  [IV Fosfomycin = £6720]
- Prolonged IV therapy and hospital stay
  [Unable to go to OPAT]
- Minimal oral options
- Need for some therapeutic drug monitoring

Summary

- Some published evidence of the clinical impact of GNB resistance in UK on processes and quality of care and outcomes at cohort level
- At patient level, resistance complicates care and *fuels the fire*
- In 3 or 4 cases presented exposure outside of UK likely to have been relevant

The Iceberg of Gram Negative Resistance



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