Treating Multi-drug Resistant Gram-negative Infections in OPAT

Fiona Robb
Antimicrobial Pharmacist
NHS Greater Glasgow & Clyde
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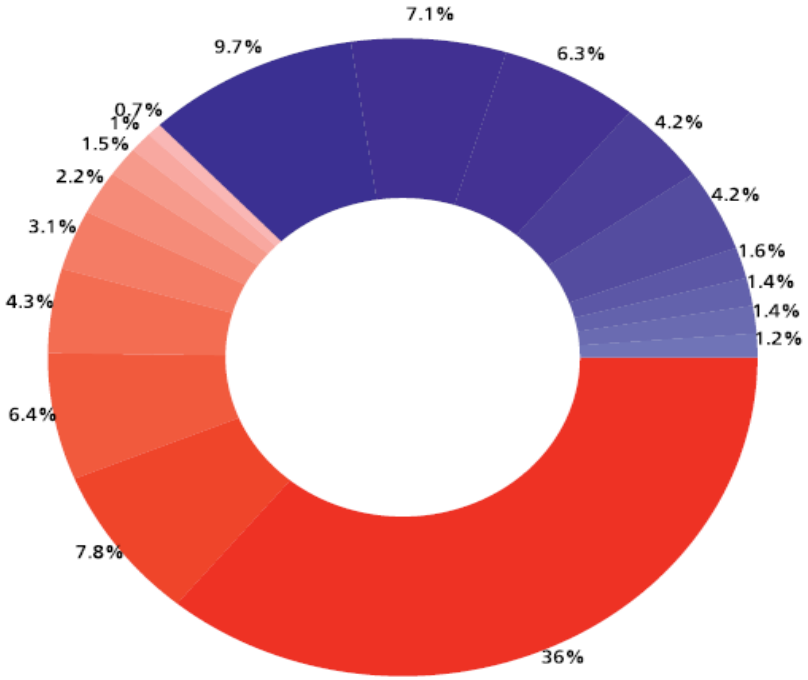
Overview

- To describe the emerging threat of Antimicrobial Resistance in particular Multi-drug resistant Gram-negative bacteria (MDRGNB)
  - the Scottish perspective
- To describe the optimal drug design for administration via OPAT services
- To summarise the challenges associated with treatment of MDRGNB infections in OPAT
  - demonstrated with patient case studies

CMO Annual Report, Infections and the Rise of Antimicrobial Resistance 2013

Figure 1.1: Organisms causing blood stream infections in adults in England, Wales and Northern Ireland, April 2011-March 2012



Gram negative
- Eschericha coli - 36%
- Klebsiella spp. - 7.8%
- Other Gram-negative - 6.4%
- Pseudomonas spp. - 4.3%
- Proteus spp. -3.1%
- Enterobacter spp. - 2.2%
- Bacteroides spp. - 1.5%
- Serratia spp. - 1.0%
- Acinetobacter spp. - 0.7%

Gram positive
- Staphylococcus aureus (MSSA) - 9.7%
- Non-pyogenic streptococci - 7.1%
- Enterococcus spp. - 6.3%
- Streptococcus pneumoniae - 4.2%
- Other Gram-positive - 4.2%
- Staphylococcus aureus (MRSA) - 1.6%
- Group B Streptococci - 1.4%
- Group A Streptococci - 1.4%
- Diphtheroids - 1.2%

Ticking time bomb…

Apocalyptic scenario…

UK Five Year Antimicrobial Resistance Strategy, 2013 – 2018

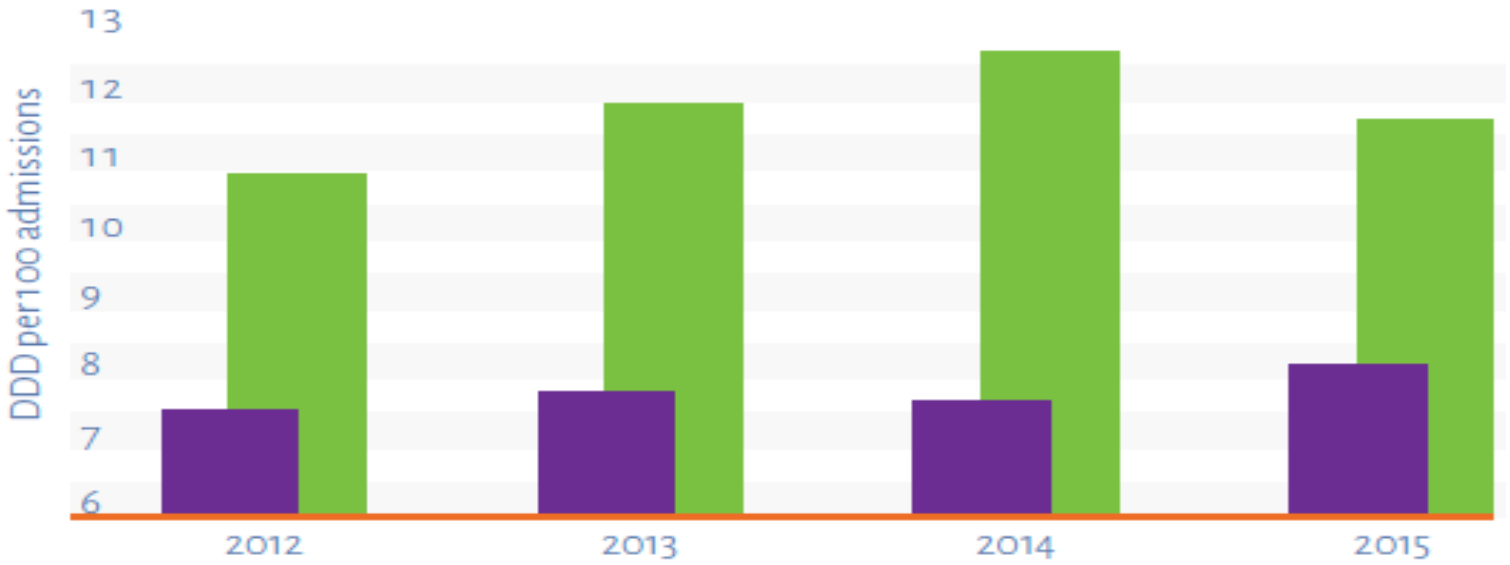
- The report has 3 main strategic aims:
  - Improve the knowledge and understanding of AMR (increased knowledge and education)
  - Conserve and steward the effectiveness of existing treatments
  - Stimulate the development of new antibiotics, diagnostics and novel therapies
- The aims are underpinned by 7 key areas:

  2. Optimising prescribing practice

Promote RIGHT drug, dose, time and duration

Scottish Antimicrobial Use and Resistance in Humans, 2015

Very broad spectrum antibiotics



Carbapenems **6.5%** increase in **2015**

Piperacillin-tazobactam **7.9%** decrease in **2015**

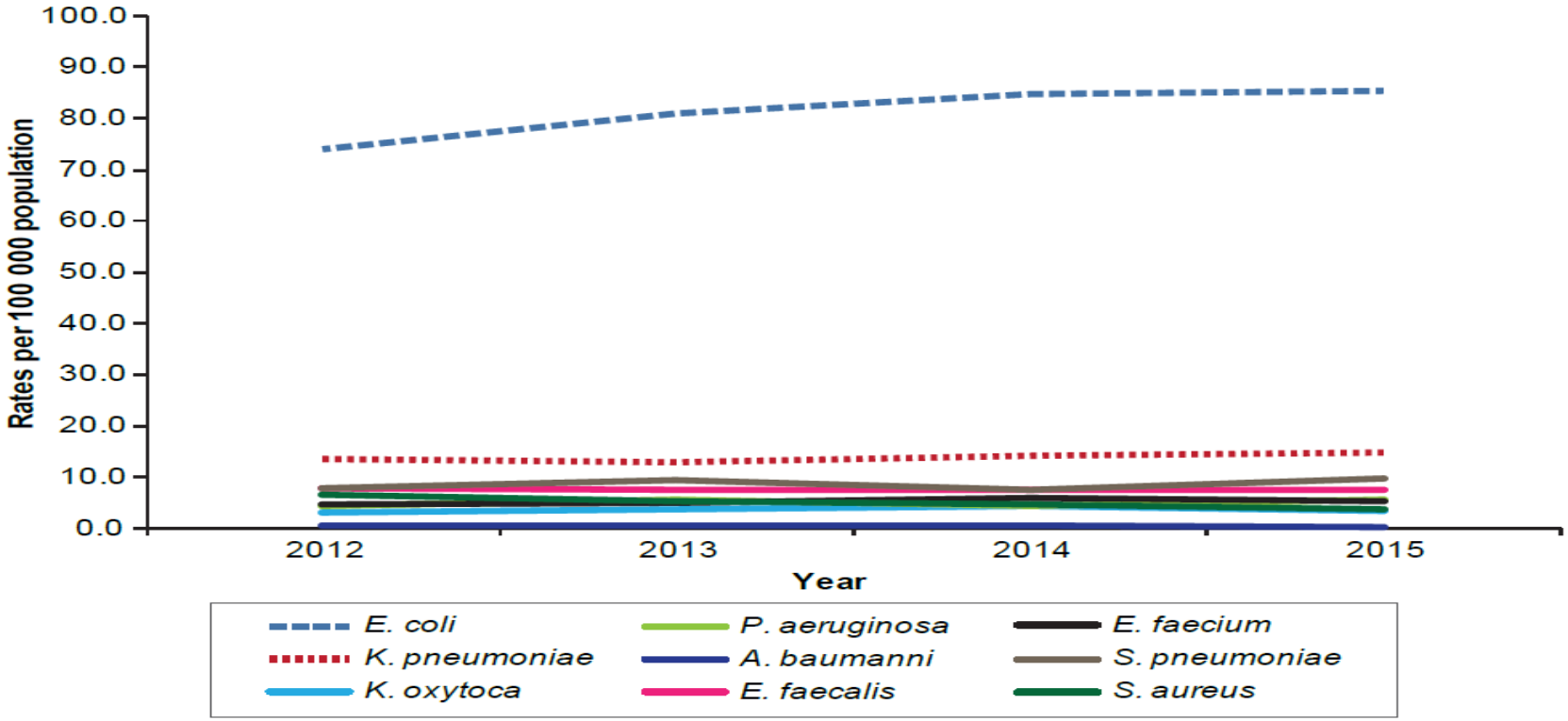
Health Protection Scotland

ISD SCOTLAND

Scottish Antimicrobial Prescribing Group

Scottish Antimicrobial Use and Resistance in Humans, 2015

Figure 3 Incidence of bloodstream infections due to the most commonly reported pathogens, 2012 to 2015.



Health Protection Scotland

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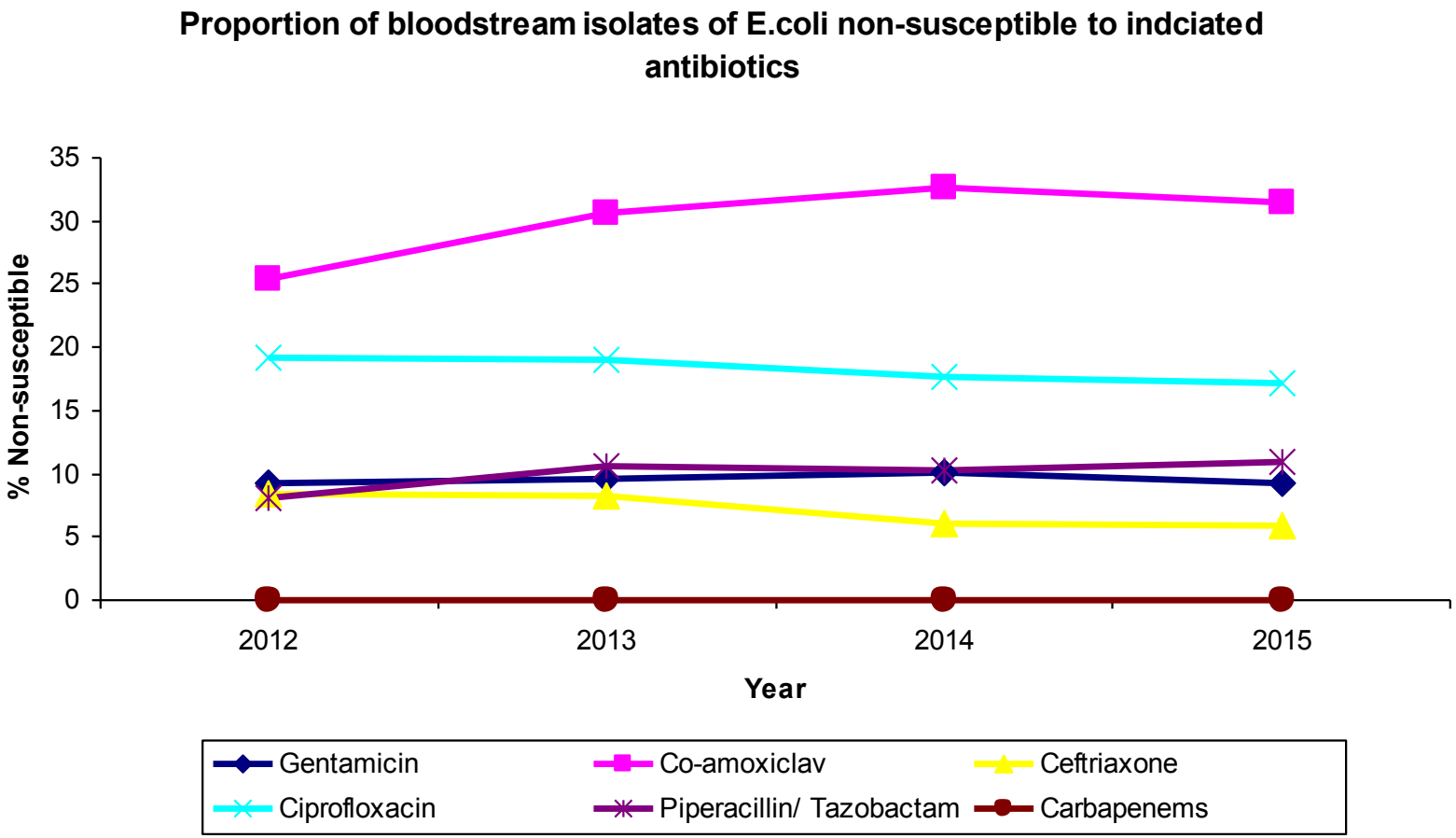

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Optimising Antimicrobial Prescribing in MDRGNB infections, 2016

- **Support** clinical management of Gram negative infections
- **Reduce** emergence of MDRGNB
- **Promote** more judicious use of broad spectrum antimicrobials
  - Review daily and documented 72 hour review
  - Rationalise according to cultures and sensitivities
- **Protect** and **preserve** the carbapenem and other key classes of antibiotics
  - Use narrow spectrum antibiotics
  - Ensure optimal pharmacokinetics/ pharmacodynamics characteristics

OPAT Good Practice Recommendations, 2012

- Pragmatic guidance for an effective OPAT service:

Antimicrobial management and drug delivery

- "Antibiotic selection should be based on appropriate prescribing principles rather than purely dosing on convenience"
- ***Recommendation 3.3*** *Antimicrobial choice within OPAT programmes should be subject to review by the local antimicrobial stewardship programme*

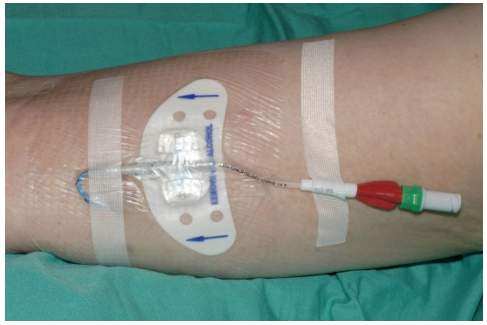
Monitoring of the patient during OPAT

- Assessment of clinical response to agreed treatment plan
- Regular/ appropriate blood monitoring (U&Es, LFTs, FBC), therapeutic drug monitoring etc.

OPAT services should provide treatment that is "at least as equivalent to inpatient care"

OPAT Antimicrobial Management Challenges





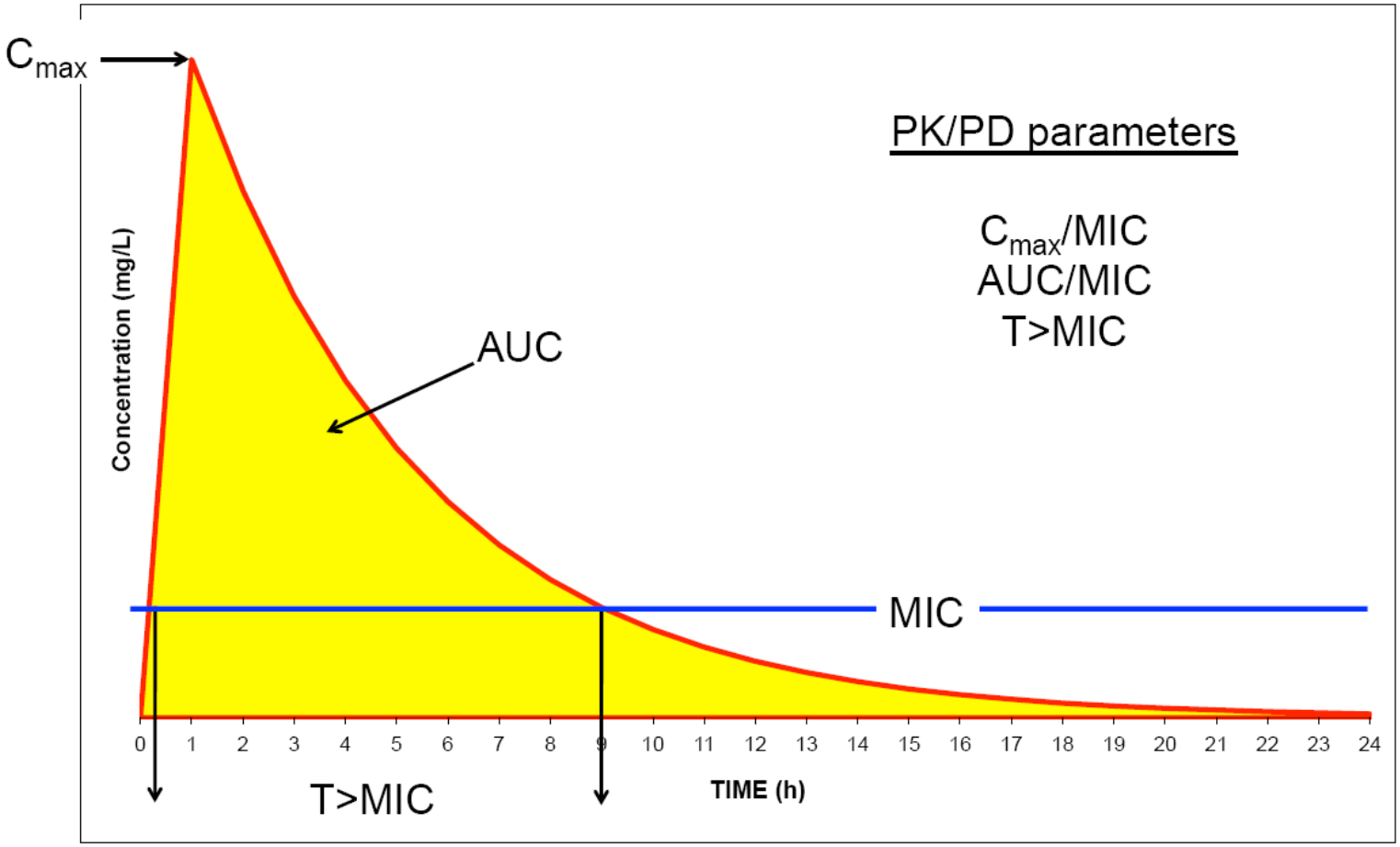

Patient factors

- Allergy
- Renal/ hepatic function
- PMHx and concomittant drugs
- Drug/ food interactions
- Self administration vs attending OPAT
- Pregnancy/ Breast feeding
- Line hygiene

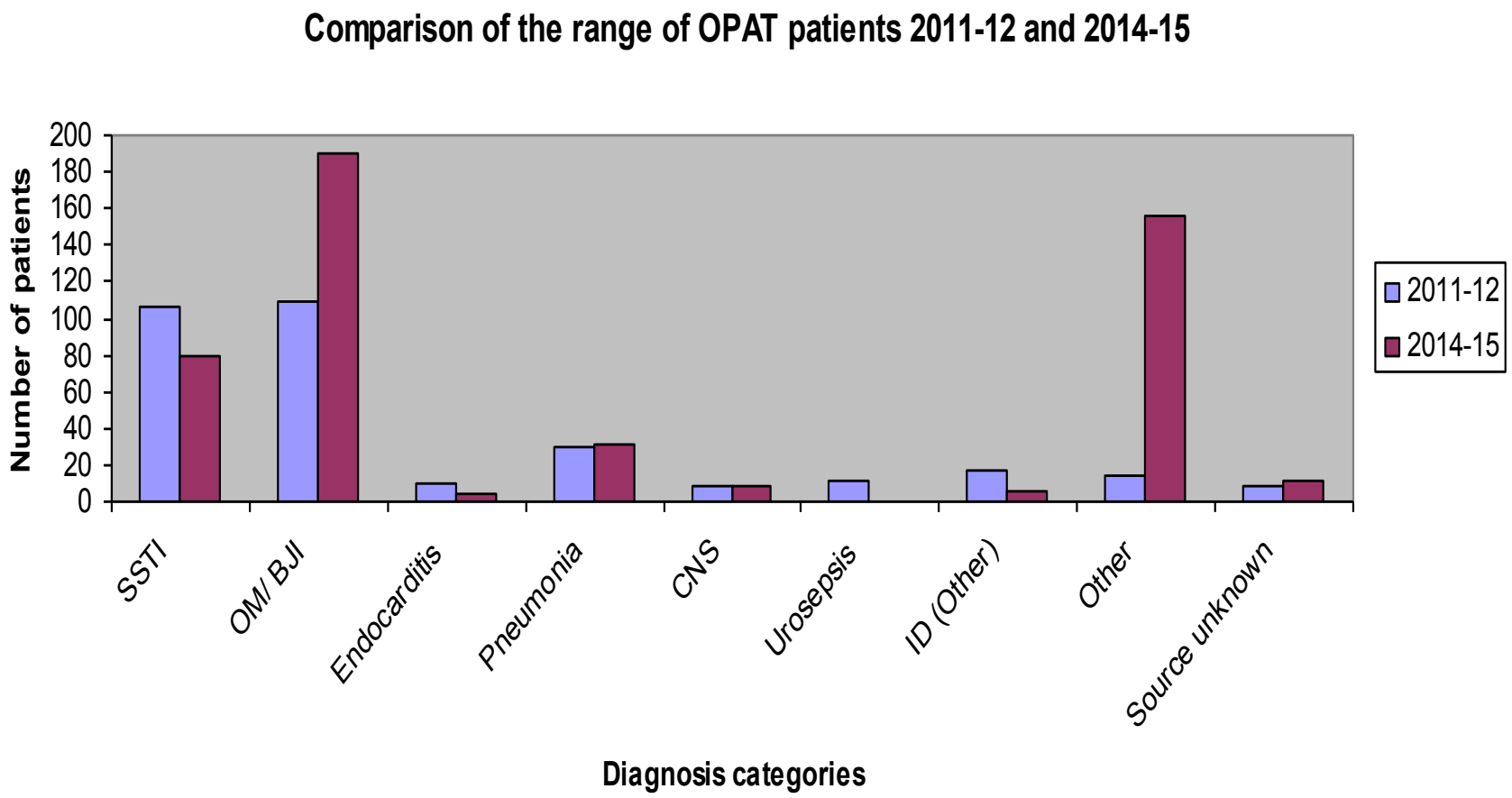
Antibiotic factors

- Spectrum of activity
- Mechanism of action
- Pharmacokinetics (PK)/ Pharmacodynamics (PD)
- Therapeutic drug monitoring
- Method of administration
- Stability/ storage requirements
- Unlicensed doses/ preparations

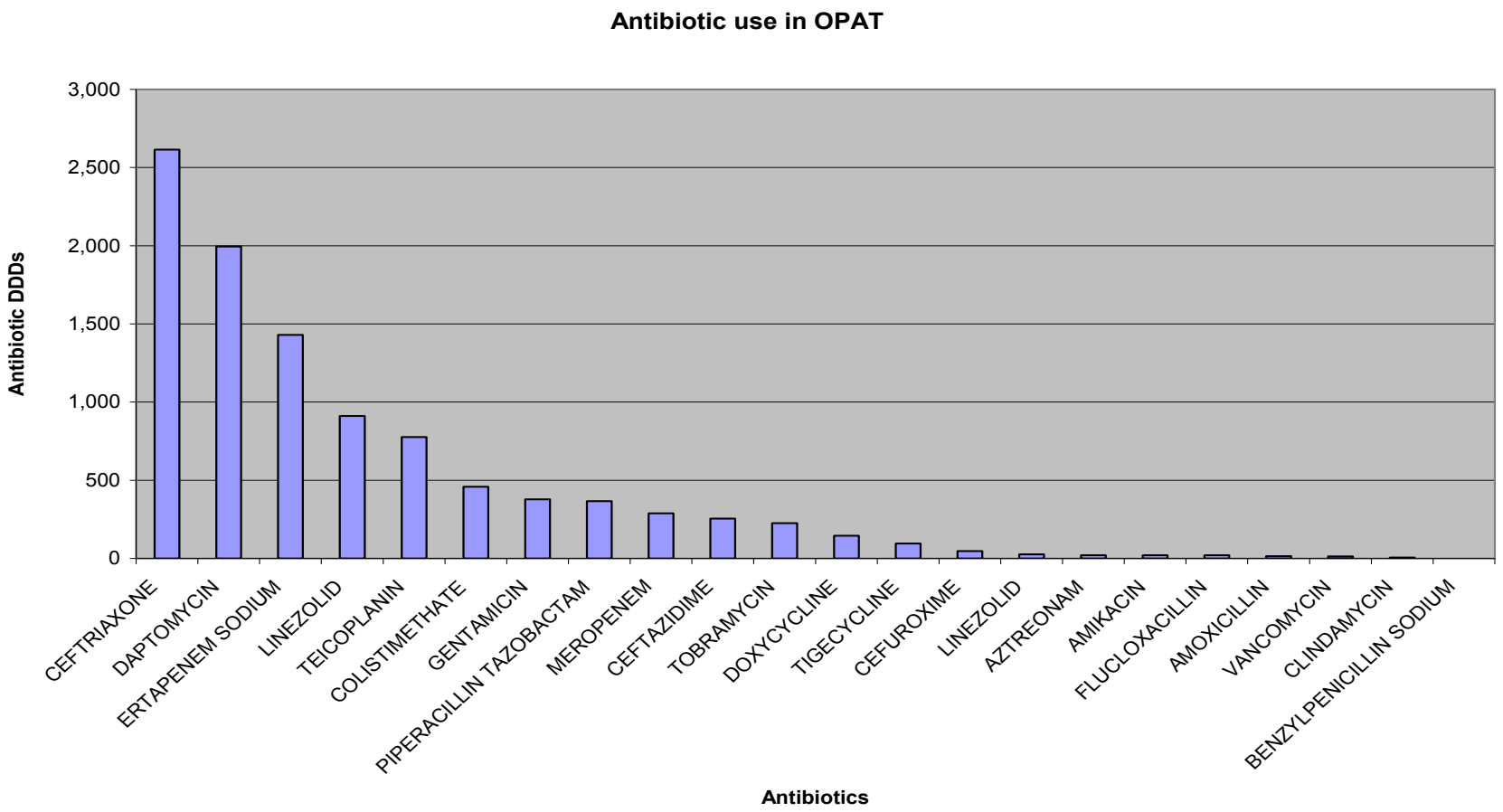
PK / PD Principles



Range of GG&C OPAT patients



GG&C OPAT Antimicrobial Usage, 2015



Case examples

Case 1: Patient AR

PMHx
Osteoarthritis

Penicillin allergy; rash

1995	Original Right (R) Total Knee Replacement (TKR)
~ 2000	One stage R TKR
2003/4	1st and 2nd
2009	2 x Exami (EUA) and wash
03/2010	Hickman line sited in theatre and received Intra-articular Vancomycin

Chronic inflammation/ neuropathic R knee pain.
No positive microbiology.

1st OPAT episode

Intra-articular Vancomycin 500 mg 12 hourly

Case R

Fell on holiday post 2nd stage TKR

Suffered a stress fracture patella

20 /13

2012 R knee tissue;
Staphylococcus saprophyticus – *R to* penicillin, *S to* flucloxacillin, vancomycin
R knee wound swab;
***Staphylococcus aureus* (MSSA)** x 3 – *R to* penicillin, *S to* flucloxacillin, vancomycin, rifampicin, sodium fusidate

2013

2013 R knee fluid x 2;
MSSA – *R to* penicillin, rifampicin, sodium fusidate, *S to* vancomycin, ciprofloxacin, clindamycin, teicoplanin, daptomycin
R knee tissue x 4; **MSSA** – As above
R knee tissue;
Staphylococcus capitis – R to
vancomycin, ciprofloxacin, clinda

Recurrent prosthetic knee joint infections.

2nd OPAT episode

Intra-articular Vancomycin 500 mg 12 hourly

Case 1: Patient AR

3rd OPAT episode

IV Daptomycin +
Po Clindamycin

10/2013	Wound still leaking +++
01/2	
2014	2 and W/O

2014 R knee fluid & wound swab;
Enterococcus faecalis – *R to* penicillin, doxycyline, *S to* amoxicillin, vancomycin, tigecycline (MIC 0.094 mg/L), daptomycin (MIC 2 mg/L)
Staphylococcus epidermidis – *R to* sodium fusidate, rifampicin, teicoplanin, *I to* doxycycline, *S to* vancomycin, ciprofloxacin, clindamycin, daptomycin.
R knee wound swab;
Streptococcus mitis/oralis – *S to* amoxicillin, ceftriaxone

Case 1: Patient AR

06/20

2014 R knee tissue;
Morganella morganii – *R to* co-amoxiclav, cefuroxime, colistin (MIC 32 mg/L), *I to* cefoxitin, *S to* ceftazidime, tigecycline, piperacillin/tazobactam, meropenem, gentamicin, fosfomycin
Enterococcus faecalis – *R to* penicillin, doxycyline, *S to* amoxicillin, vancomycin, daptomycin, tigecycline, fosfomycin
R knee fluid;
Morganella morganii – As above,
***Escherichia coli* (ESBL)** – *R to* co-amoxiclav, gentamicin, ciprofloxacin, cefoxitin, temocillin, piperacillin/tazobactam, *I to* amikacin, *S to* meropenem, tigecycline, colistin (MIC 0.125 mg/L), fosfomycin

4th OPAT episode

IV

4th OPAT episode continued .....

IV Fosfomycin 8g 8 hourly

Tigecycline

Class: Glycylcycline, related to the tetracycylines

Mechanism of action

- Bacteriostatic
- Inhibits bacterial protein synthesis

Broad spectrum of activity

- MRSA, VRE, Penicillin resistant *S. pneumoniae*
- ESBL producing GN bacteria
- Limited activity against *Morganella sp.* and *Proteus*

Resistance mechanism

- Plasmid mediated efflux pump and ribosomal protection

Tigecycline

Pharmacokinetic/ Pharmacodynamic parameters

Absorption	Distribution	Metabolism	Excretion
100 %	80 % protien binding Vd 7 – 10 L/kg Distributes to tissue, bone, lungs, gallbladder, colon etc	< 20 %	~ 60% unchanged via biliary excretion

- t½ ~ 42 hours at steady state, PAE ~ 0.7 – 5 hours for GNB
- Time dependent, AUC/MIC

Potential adverse drug reactions

- Gastrointestinal disturbances are common
  - Nausea and vomiting (1/10 patients), diarrhoea
- Teeth staining and inhibition of bone growth
- Deranged liver function tests

Clin Pharmacokinet, 2009; 48 (9): 575 – 584

J Antimicrob Chemother, 2008; 62 (Suppl 1): i11 – i16

Tigecycline

Dose administration

- Loading dose 100mg IV then Maintenance dose 50mg 12 hourly IV (100 mg 12 hourly in CPE)
- No dose adjustments in renal impairment
- Clearance ↓, Half-life ↑ in severe liver impairment; half maintenance dose

……Future OPAT dosing

- Favourable AUC/MIC, long half-life and PAE
- Loading dose followed by 100mg IV infusion 24 hourly
- Limited by adverse effects

Eur J Clin Microbiol Infect Dis, 2016; 35: 1673 – 1677

Antimicrob Agents Chemother, 2009; 53 (2): 782 - 784

Fosfomycin

Mechanism of action

- Bactericidal
- Inhibits bacterial cell wall synthesis leading to cell lysis

Broad spectrum of activity

- Good activity against MSSA, MRSA, *E.coli* (ESBLs)
- Reasonable activity against *Enterococcus sp*
- Limited activity for *Morganella sp*

Resistance mechanism

- Chromosomal mutations reduce drug transport into cell
- Plasmid mediated drug inactivation
- Combination therapy is usually recommended

Fosfomycin

Pharmacokinetic/ Pharmacodynamic parameters

Absorption	Distribution	Metabolism	Excretion
100 %	Virtually no protein binding Vd 15 – 30 L Distributes to eyes, bones, muscle, interstitial fluid, bile	Not metabolised	Excreted in urine and faeces unchanged

- Short t½ ~ 2 hours , PAE ~ 4 hours
- Concentration dependent killing for GNB,
- Time dependent for *Staphylococcus aureus sp*

Potential adverse drug reactions

- Generally well tolerated; headache, abdominal pain, deranged liver function tests
- Electrolyte disturbances; 8g vials contain; 2.56 g/ 111mmol of sodium

Int J of Infect Dis, 2011; 15: e732 – 739

Int J of Antimicrob Agents, 2009; 34: 506 - 515

Fosfomycin

Dose administration

- IV formulation for systemic infections; 16 – 24 g/ 24 hours divided into 6 – 8 hourly intervals
- Dose reduction in renal impairment

……Future OPAT dosing

- T > MIC for 40 – 70 % of dosage interval (70 – 100 % in critically ill patients)
- Use high daily doses; 24g in 24 hours
- ? Limited to Gram-positive infections and *Pseudomonas sp*

J of Cys Fibrosis, 2007; 6: 244 - 246

Int J of Infect Dis, 2016; 50: 23 – 29

Case 1: Patient AR

2014/15	Successful 1st and 2nd stage R TKR

- Fosfomycin used as orthopaedic surgical prophylaxis
- No admissions/ infections 2016

? OPAT patient mentor

Case 2: Patient RR

Patient RR (21 year old male), 2012

- Penicillin allergy, No relevant PMHx/ DHx

- Attended G.P. 1 month previous
  - Left ear pain, discharge
  - Prescribed Gentisone HC® ear drops, symptoms resolved
- Presented to Out of Hours (Day 1)
  - ↑ pain, discharge, itch, deafness left ear
  - Red, inflammed pinna and tympanic membrane (intact)
  - Clinically stable, SIRS 1 (HR)
  - Diagnosis; Otitis externa
- Clinical plan:
  - Ear swabs, daily irrigation
  - Meropenem 1g 8 hourly IV + Gentamicin 0.3% ear drops (2drops 6 hourly)

Case 2: Patient RR

Patient RR continued

- Day 3
  - No significant clinical improvement
  - CT; no evidence of malignant otitis externa
  - Ear swabs: *Pseudomonas aeruginosa*; *R to* meropenem, gentamicin, tobramycin, ciprofloxacin, chloramphenicol, *S to* piperacillin/tazobactam, ceftazidime, colistin
- Clinical plan:
  - Ceftazidime 2g 8 hourly IV + Colistin (LD; 3 MU 12 hourly, MD; 2 MU 8 hourly) IV
  - Discharged home via OPAT to complete 6 weeks IV antibiotics

Case 2: Patient RR

Patient RR continued

- Day 10; Colistin plasma concentrations obtained
  - Trough; 2 mg/L (2 – 6 mg/L)
  - 1 hour post dose; 6.8 mg/L (10 – 15 mg/L)
  - MD increased to 3 MU 8 hourly IV
  - Patient unreliable for further levels

- Patient clinically improved, completed OPAT

Colistin

Class: Polymixin

Mechanism of action

- Bactericidal
- Colistimethate sodium salt (CMS) is a prodrug for active colistin
- Increased permeability of the outer membrane leading to leaking of intracellular contents and cell death

Narrow spectrum of activity

- No activity against Gram-positive bacteria
- Good activity against Gram-negative bacteria; *E. coli, Klebsiella sp, Pseudomonas sp, Acinetobacter sp.*

Mechanism of resistance

- Unclear ? Decreased binding to outer membrane, efflux pumps, colistinase enzyme

Colistin

Pharmacokinetic/ Pharmacodynamic parameters

Absorption	Distribution	Metabolism	Excretion
100 % CMS	? 50 % protein bound	CMS is a prodrug of Colistin	CMS is renally cleared Colistin has non-renal excretion

- Not fully understood;
  - concentration dependent killing, AUC/MIC

Potential adverse drug reactions

- Nephrotoxicity; not as toxic as previously thought, mechanism not fully understood
- Neurotoxicity; manifests as dizziness, confusion, headache, muscle weakness, parasthesia, visual disturbances, seizures
  - ? Related to dose, infusion rate

Antimicrob Agents Chemother, 2011; 55: 3284-94
South African Med J, 2014; 104 (3): 183 – 186

Colistin

Dose administration

- 1mg colistin base activity is contained in 2.4 mg CMS which is equivalent to 30, 000 IU of CMS
- Traditional vs New dosing……..

Body Weight	Loading Dose (LD)	Notes
> 50 kg	9 Million Units	In obese patients (BMI > 30) use ideal body weight.
≤ 50 kg	6 Million Units	

Creatinine Clearance	Maintenance Dose and Frequency	Starting time after LD
≥ 50 ml/min	4.5 Million Units 12 hourly	12 hours
30 – 49 ml/min	3 Million Units 12 hourly	24 hours
10 – 29 ml/min	2.5 Million Units 12 hourly	24 hours
< 10 ml/min	1.75 Million Units 12 hourly	24 hours

Colistin

Therapeutic drug monitoring required

- Samples are sent to the Antimicrobial Reference Laboratory, Bristol
- New Colistin assay available
- Trough 2 – 4 mg/L

……Future OPAT dosing

- PK/ PD knowledge is limited
- LD then 24 hourly dose in 1, 2 or 3 divided doses
- Once, twice daily administration limited by resistance

J of Antimicrob Chemother, 2008; 61: 636 - 642

Crit Care, 2010; 14 (Suppl 1): Abstract

NPSA risk category: Amber

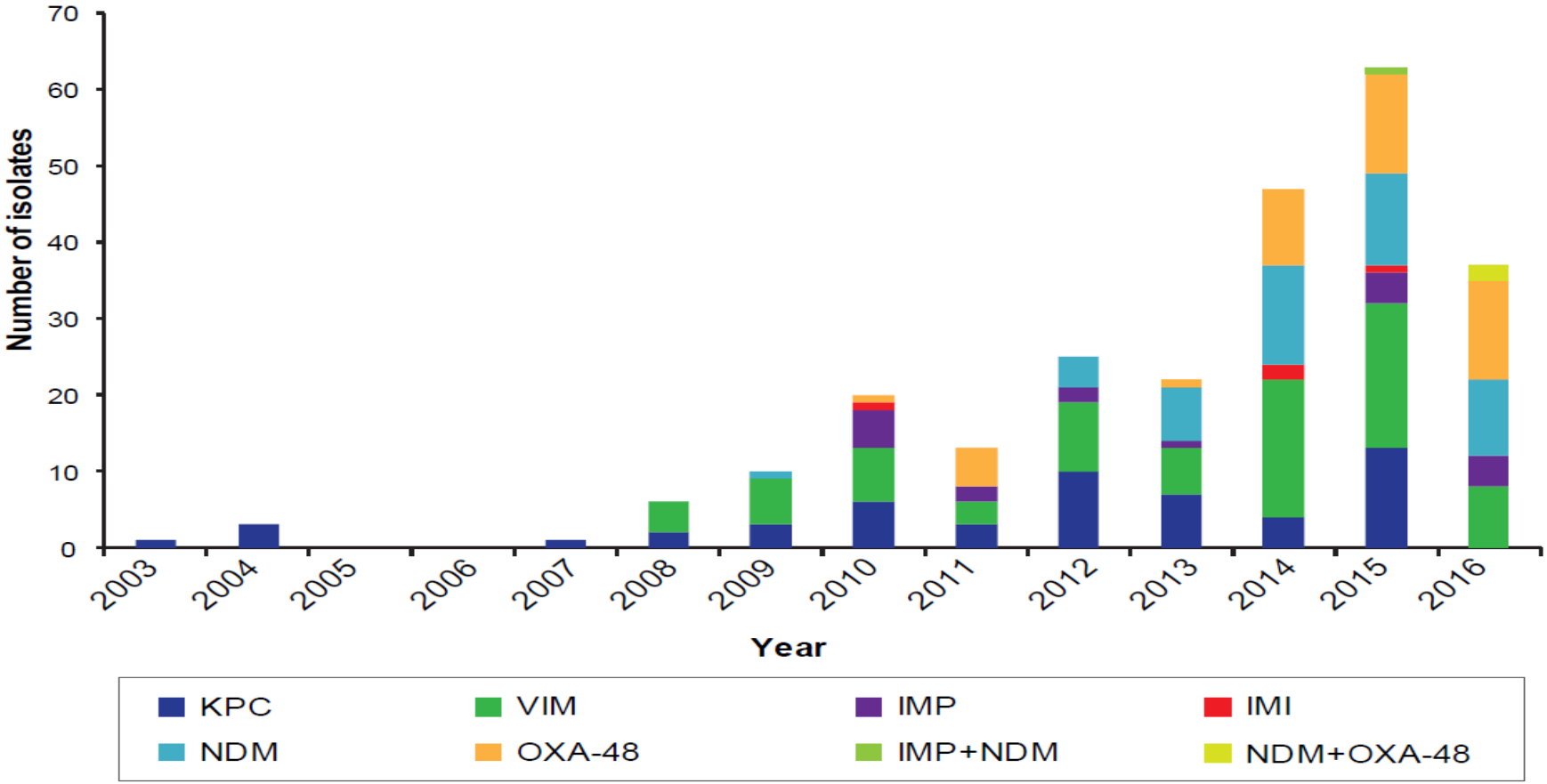
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]econstitution
- [illegible] irritant to
- [illegible]
- Clear s[illegible]
- Reconstituted solution has high osm[illegible] irritant to veins

Colistin

- NPSA risk category; AMBER
- Roll in hand (avoid shaking) to reconstitute

The Future…….

Figure 4 Total number of carbapenemase enzymes, 2003 to 2016 (2016 data until end of June).



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New agents against CPOs

Antibiotic	Class	KPC	OXA-48	MBL
Ceftazidime/ avibactam	β-lactam – DBO			
Meropenem/ vaborbactam	β-lactam – boronate			
Eravacycline	Tetracycline			
Imipenem/ relebactam	β-lactam – DBO			
Plazomicin	Aminoglycoside			
Aztreonam/ avibactam	β-lactam – DBO			
Temocillin	β-lactam			

Professor Livermore; FIS 2016

Summary

- Antimicrobial resistance is increasing globally, across Europe and in our local hospitals
- MDR GNB are the most prevalent reported blood stream infections
- Antimicrobial stewardship programmes promote "Right drug, dose, time and duration"
- OPAT services should provide treatment that is "at least as equivalent to inpatient care"
- OPAT can rise to the challenge