Oral antibiotics are not always straight forward

OPAT Regional Workshop
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Introduction

- Describe NHS GGC's Oral vs IV Antibiotics (OvIVA) trial experience
- Describe the optimal oral antibiotic choice for administration via OPAT
- Summarise the challenges associated with the choice of oral antibiotics for OPAT

Oral vs IV Antibiotics (OvIVA) Trial

Within NHS each year:

- 120,000 joints & fracture procedures (BJIs)
  - ~2000 (2 %) post-op infection
- ~5000 diabetic foot osteomyelitis/infections (DFIs)
  - Cost £20 – 40,000 per patient
- Current 'gold standard' practice; 4 – 6 weeks IV therapy
- Emerging evidence & Cochrane review support oral antibiotics for treatment of these infections BUT small trials

Study design

- Multi-centre, randomised, open label, non-inferiority trial
- Randomised within ONE week of diagnosis/ starting IV therapy

Oral vs IV Antibiotics (OvIVA) Trial

Inclusion criteria

- Bone & Joint infection (native and prosthetic joint)
- Diabetic patients with soft tissue/ bone infections
- Traditionally required at least SIX weeks of IV antibiotics

Exclusion criteria

- Staphylococcus bacteraemia/ endocarditis
- TB/ Fungal/ Parasitic infections

Endpoint

- Treatment failure (microbiology/ histology/ clinical)
- Serious adverse drug reaction/ intolerance
- Line complications

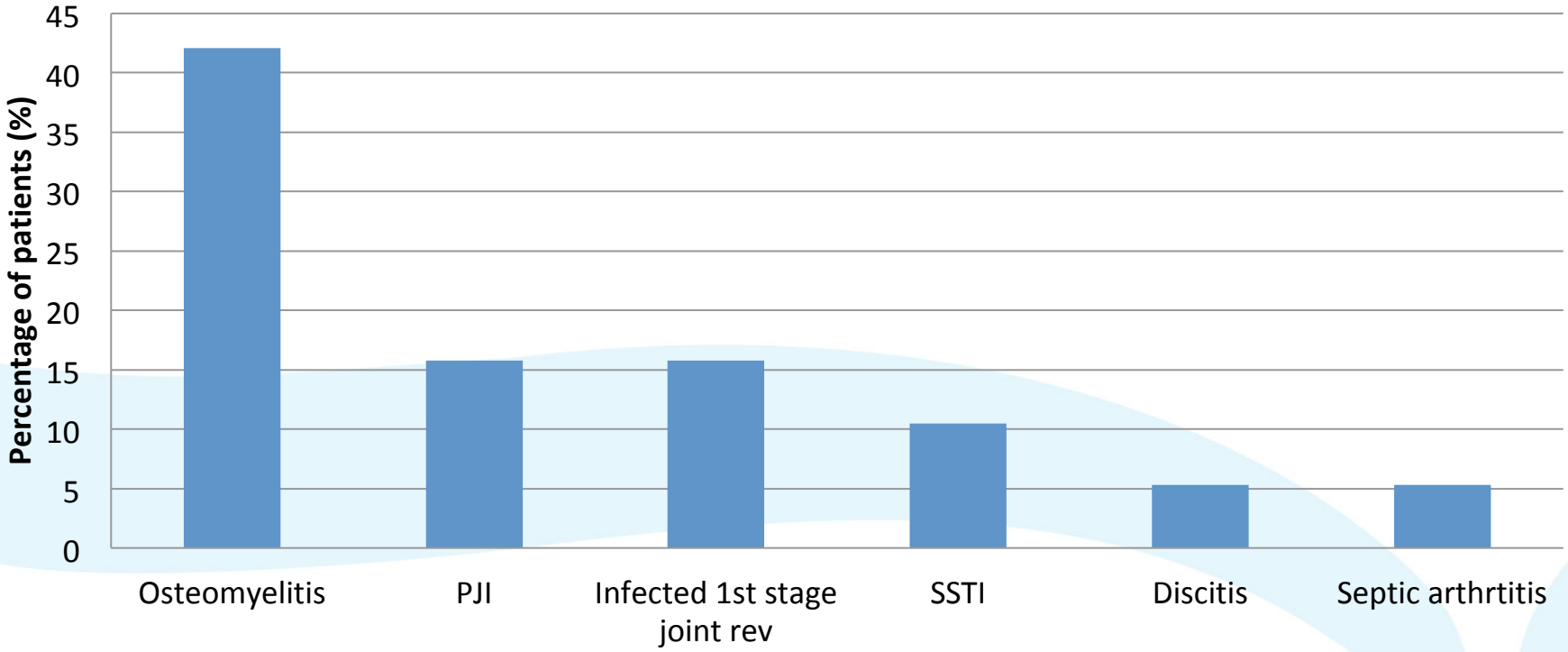
Oral vs IV Antibiotics (OvIVA) Results

- 1054 randomised patients (Sample size > 1050)
  - Across 26 UK centres
  - Randomised evenly between IV/ oral groups
- Non-inferiority observed between IV and Oral treatment groups
- Represents major implications for practice
  - Choice of oral antimicrobial agent
  - Safe monitoring for toxicity/ efficacy
  - Patient follow up

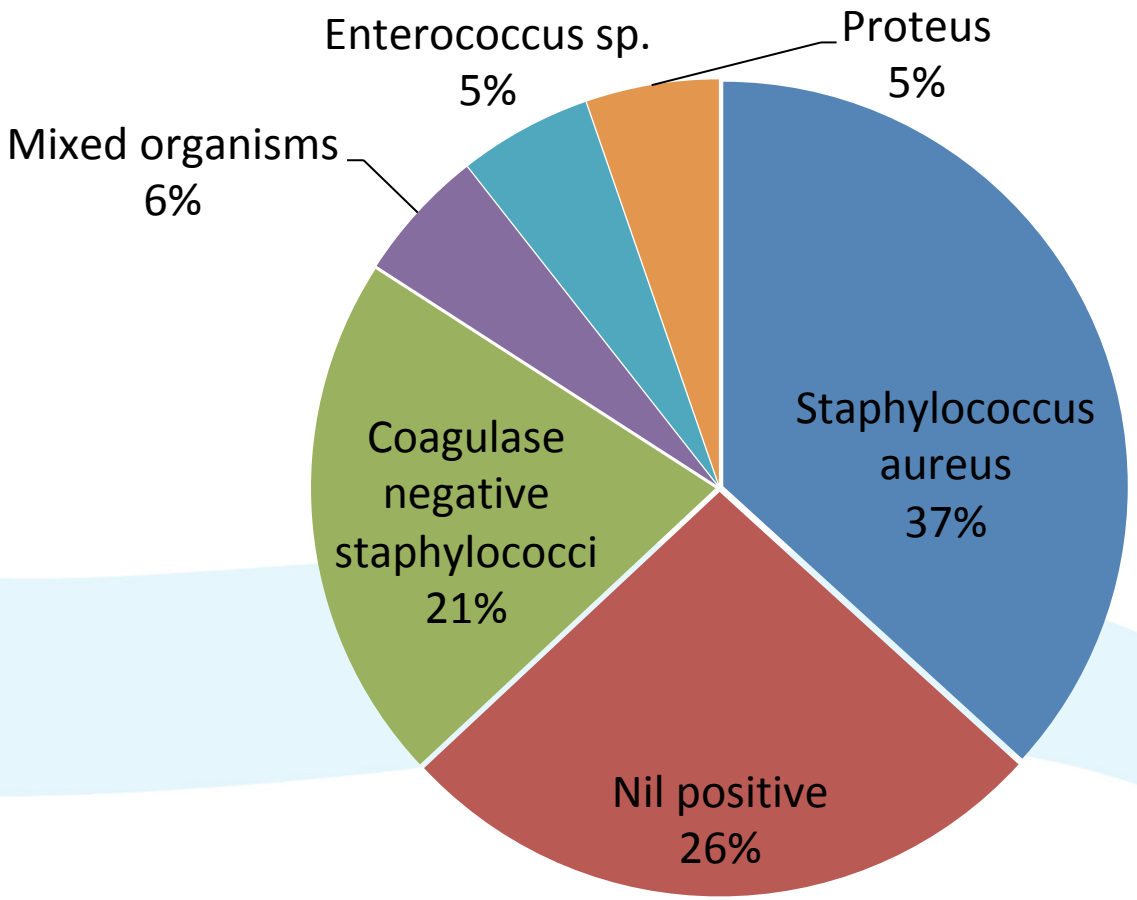
NHS GGC's OvIVA Results

- Total 43 patients participated in OvIVA
  - 19 Randomised to ORAL therapy
  - 13 Male (6 Female)
  - Median age 53 years (range 30 – 83)
  - Median number of prior IV days; 6 (range 0 – 7)
    - 3 patients received > 7 days IV therapy; wards failed to switch patient as planned
  - Median intended duration of therapy; 8 weeks (range 6 – 24 weeks)
    - 1 patient remained on long-term antibiotics (18 months)
  - 17 patients reviewed at 14, 42, 120 & 365 days
    - 1 patient re-admitted, 1 patient unable to contact at 365 days

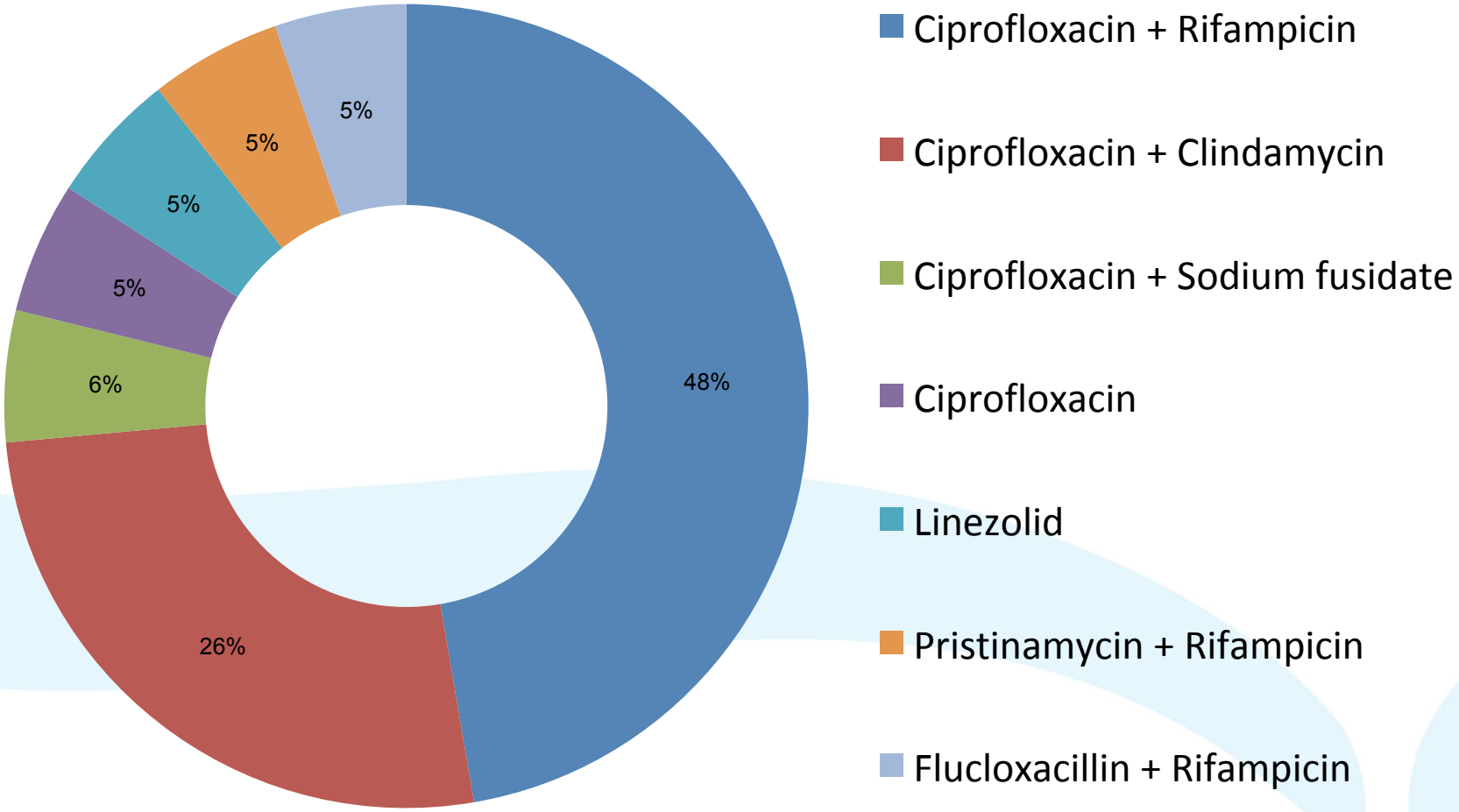
NHS GGC's OvIVA Results; Range of OvIVA indications



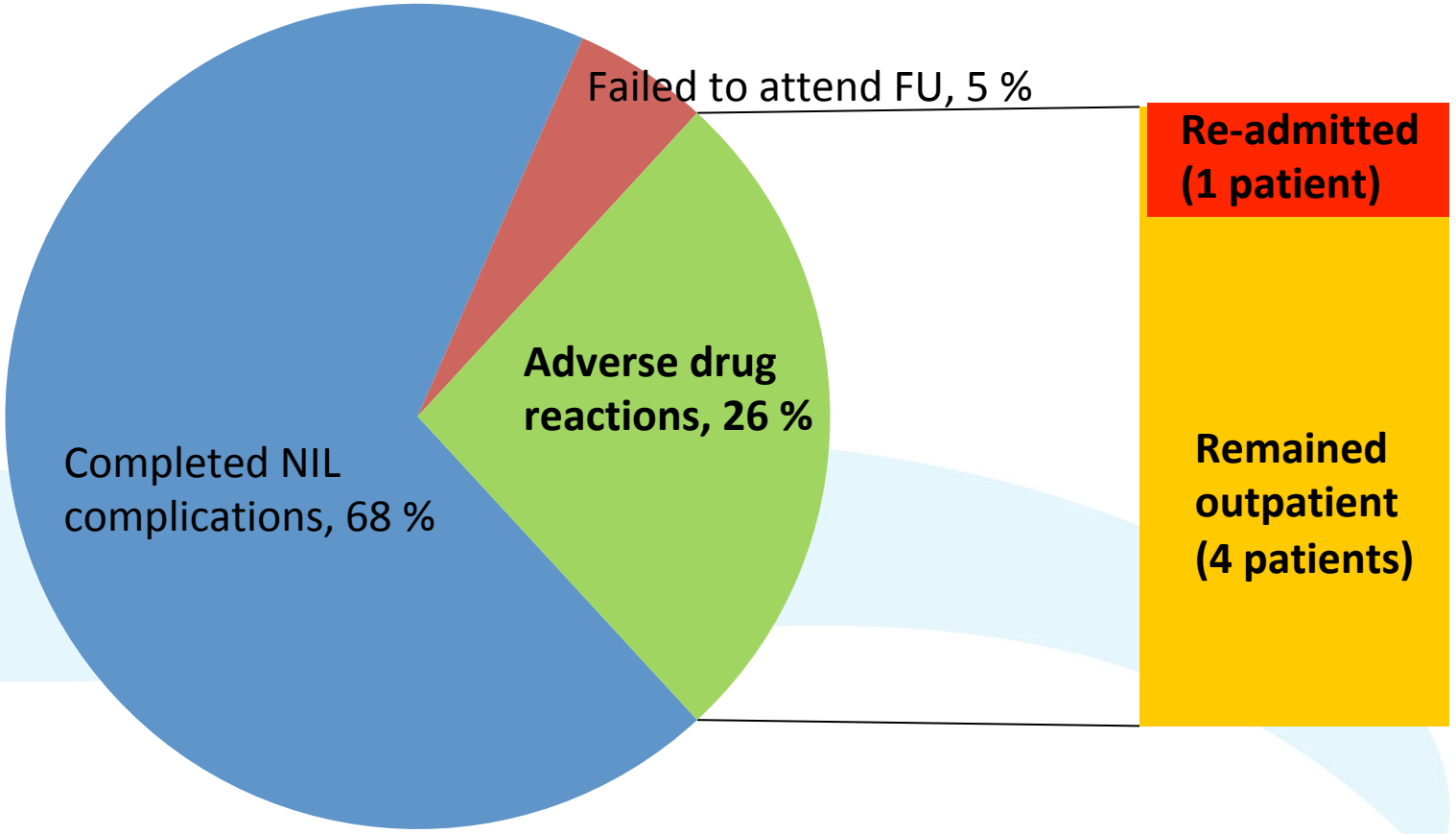
NHS GGC's OvIVA Results; Microbiology identified



NHS GGC's OvIVA Results; Range of antibiotic therapy



NHS GGC's OvIVA Results; Patient outcomes



NHS GGC's OvIVA Results; Additional oral antibiotic considerations

- Two thirds of patients (63%) had potential drug interactions
  - Quinolones + calcium/iron supplements
  - Rifampicin + analgesia/ anti-diabetic/ cardiovascular drugs
- 1 in 2 patients (53%) required additional/ increased monitoring
- 1 in 5 patients (21%) required outpatient ECGs
  - Quinolones + SSRIs/ TCAs
- Changes to regular medication (1 patient, 5%)
  - Developed AKI; loop diuretic , ACE inhibitor and metformin stopped

Optimal Pharmaceutical Care in OPAT?

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
  - Antimicrobial choice 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”

A Chapman et al. JAC, 2012; 67: 1053 – 1062.

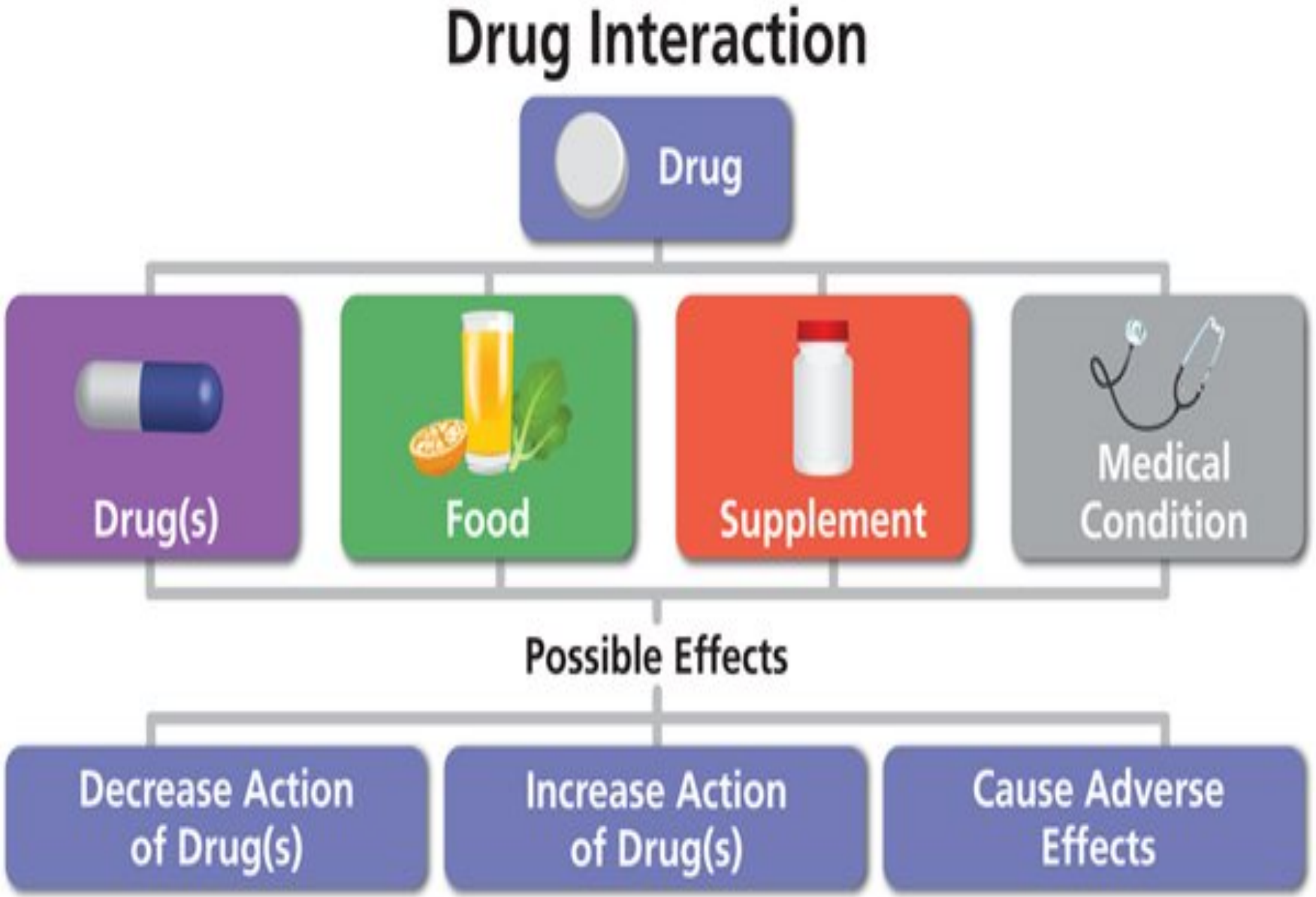
Oral Antimicrobial Management Challenges

Patient factors

- Allergy
- Renal/ hepatic function
- PMHx and concomittant drugs
- Drug/ food interactions
- Pregnancy/ Breast feeding

Antibiotic factors

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



https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/95/what-is-a-drug-interaction-

Example of a patient seen in Glasgow's OPAT service

Patient Example

- 34 yr old female, osteomyelitis R distal femur
- Joint aspirate; MRSA
  - Resistant to rifampicin, clindamycin, doxycycline
  - Sensitive to ciprofloxacin, linezolid, sodium fusidate, vancomycin, daptomycin
- PMHx; focal epilepsy since childhood
- DHx; Carbamazepine, Tramadol, Amitriptyline
- Social Hx; UK resident 2 years, limited English, lives at home with husband and 2 children
- Commenced on IV Vancomycin as inpatient

Patient Example

- Erratic and sub-therapeutic vancomycin concentrations
- Arranged interpreter to discuss desirable treatment outcomes/ optimal vancomycin dosing
  - Patient absent from ward
  - Nurse expressed ‘she’s disconnected her pump again!’
- Treatment options to complete 12 weeks therapy
  - Optimise IV Vancomycin as inpatient
  - Discharge via OPAT on suitable antimicrobial regimen

MHRA Carbamazepine advice, 2009

Drug safety advice

Antiepileptics: adverse effects on bone

Keywords: antiepileptics, carbamazepine, phenytoin, phenobarbital, primidone, sodium valproate, bone mineral density, osteopenia, osteoporosis, osteomalacia, fractures

The available data suggest that long-term use of carbamazepine, phenytoin, primidone, and sodium valproate is associated with decreased bone mineral density that may lead to osteopenia, osteoporosis, and increased fractures in at-risk patients. Vitamin D supplementation should be considered for at-risk patients who are taking these medicines long term

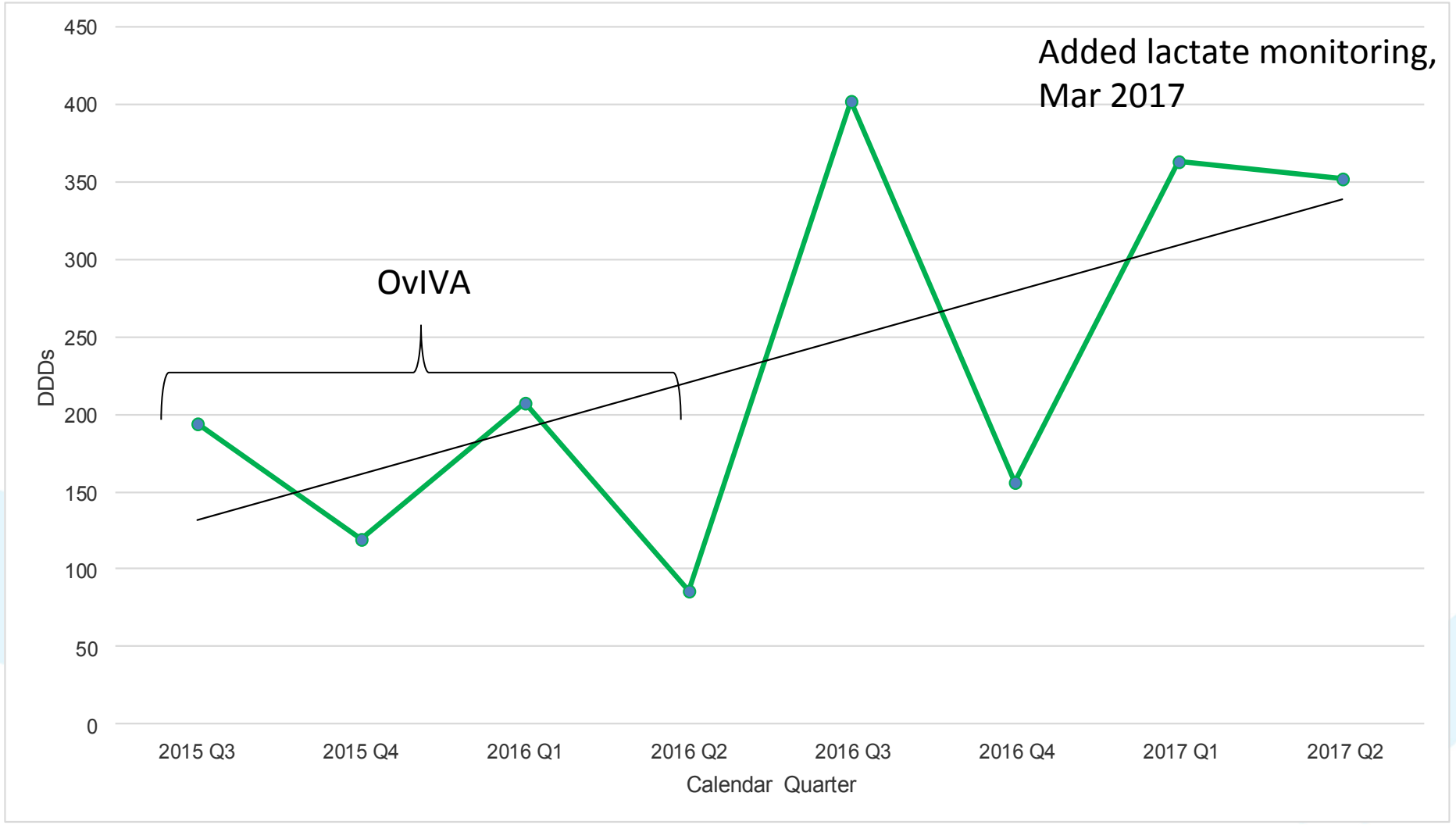
Serum (non-adjusted) calcium low, Vitamin D levels not checked.

Patient Example

- Options via OPAT to complete 12 weeks therapy?
  - IV Daptomycin + Po Sodium fusidate
  - Po Linezoild + Po Sodium fusidate

- Linezolid + carbamazepine
  - Liaised with neurology to change anti-epileptics
- Linezolid + tramadol + amitriptyline
  - Gradual withdrawal and assessment of analgesia
- Linezolid monitoring
  - FBC, lactate, peripheral neuropathy, eyesight, ? TDM

GGC OPAT Linezolid Usage, Q3 2015 – Q2 2017



Oral Antibiotics

Oral Antibiotic/ Dose	Drug monitoring/ Counselling required
Rifampicin 450 mg 12 hrly	• Never prescribed as monotherapy • Numerous drug interactions (CYP 3A4) • LFTs 2 – 3 times weekly as inpatient, 2 weeks post discharge then monthly (e.g. transaminitis) • May colour all bodily fluids orange/ red colour
Doxycycline 100 mg 12 hrly	• Avoid concomitant oral iron supplements • Separate administration from Ca^{2+}, Mg^{2+}, Al^{3+}, some nutritional supplements • Risk of oesophageal/ GI ulceration; take with a large glass of water when sitting/standing • Avoid direct sunlight/ wear sunscreen
Clindamycin 600 mg 8 hrly	• Stop immediately if diarrhoea occurs during therapy

Oral Antibiotics

Oral Antibiotic/ Dose	Drug monitoring/ Counselling required
Ciprofloxacin (or Levofloxacin*) 750 mg 12 hrly (or 500mg 12 hrly)	• Numerous drug interactions (CYP1A2, not*) • Separate administration from Ca^{2+} (not*), Mg^{2+}, Al^{3+}, Fe^{2+}, Zn^{2+}, some nutritional supplements • Avoid in patient with hx of seizure activity; can lower seizure threshold • Increased risk of prolonged QTc interval • Counsel on tendonitis esp high dose, elderly pts
Linezolid 600 mg 12 hrly	• See NHS GGC guidance (IPC protocol) • Weekly monitoring including FBC, lactate • Risk of serotonin syndrome; SSRIs, TCAs etc • Optic neuropathy; stop if changes in eyesight • Peripheral neuropathy > 28 days prescribe pyridoxine 10 – 25 mg od • Licensed duration therapy 28 days

Oral antibiotic clangers!

- Rifampicin + Sodium fusidate
- Rifampicin + Linezolid
- Rifampicin + Doxycycline
- Rifampicin + DOACs/ Warfarin
- Doxycycline + oral iron supplements
- Linezolid + SSRIs/ TCAs/ MAOIs
- Quinolones + Seizure history
- Ciprofloxacin + Duloxetine

Summary

- OvIVA Trial
  - Oral antimicrobial therapy non-inferior to IV therapy
  - Must continue to optimise & individualise pharmaceutical care
  - Enables patients to go home early/ Avoids admission
- OPAT service is changing
  - Gold standard care for BJI/ DFI infections is being challenged
  - Opportunity to change and expand service
- Oral antimicrobial therapy is not straight forward
  - Clinical pharmacist input is essential to support this change in practice (choice of therapy, monitoring & follow up)
  - Concern that patients may be discharged without OPAT monitoring/ follow up