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High dose ceftriaxone induced neutropenia

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Patient centred . Excellence . Respect . Compassion . Safety

Overview

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- Background
- Case studies
- Lessons learnt
- Pharmacovigilance and medication safety
- Literature search

Background

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- **Ceftriaxone is commonly used on OPAT for osteomyelitis, discitis and diabetic foot infection**
- **Most commonly used dose by the ULHT OPAT is IV 2g OD**
- **Course length is approximately 6 weeks**
- **SPC states:**
  - **FBC should be checked regularly during prolonged treatment**
  - **Close monitoring on side effects in severe renal and hepatic impairment**
  - **Common side effects include leukopenia, thrombocytopenia and eosinophilia**
  - **Agranulocytosis – frequency not known**

(EMC, 2023)

Case studies

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- Started a surveillance study on ceftriaxone induced adverse effects in Dec 2021
- Three patients were identified to have developed neutropenia out of 117 patients treated with IV ceftriaxone on OPAT between December 2021 and May 2023 (18 months)

Case study 1

- 80 year-old Caucasian lady admitted with infected right TKR
- PMH: AF, CKD, diverticular disease, bilateral THR, osteoporosis, osteoarthritis, anaemia
- A/w AKI 2 and elevated inflammatory markers (CRP, WCC, Neut); low Hb 88
- Had aspiration, washout and then first stage revision
- Abx Hx: 3/7 IV flucloxacillin; 1 dose of Tazocin; IV ceftriaxone 2g OD for 6/52; referred to OPAT
- Developed neutropenia and leukopenia on day 37; ceftriaxone was stopped on the same day
- Management: switched to IV flucloxacillin the next day; reverse isolation in SR; d/w haem – FBC on alternative days
- Investigations: felt well; NEWS 0 throughout; no new medications; no history of haem/malignancy; normal vit B12 and folate; unlikely to be undiagnosed infective causes e.g. Covid
- Outcome: No complications; quick recovery of neutropenia hence most likely ceftriaxone induced; remained well and completed 6/52 IVAB as planned

	Day 1 ceftriaxone	Day 7	Day 10 (clinically improving)	Day 14	Day 27	Day 29 ceftriaxone	Day 37 (neutropenia and stopped ceftriaxone)	Day 38 (Switched to IV flucloxacillin)	Day 42	Day 43	Day 47
Neutrophil (2.1-7.4 x 10^9/L):	12.38	12.67	9.52	5.96	4.78	2.85	0.05	0.19	3.57	6.15	5.16
WCC (4.3-11.2 x 10^9/L):	14.5	15	12.3	7.6	6	4.6	1.8	1.9	6.1	9.3	7.6

Case study 2

- 69 year-old Caucasian male admitted with sacral and rectal pain since APER procedure in Jan 2022, intermittent fever and frequent episodes of night sweats
- PMH: HPT, arthritis, anterior colonic resection 2020, APER for adenocarcinoma of rectum in 2022, multiple pelvic collections since Jan 2022
- A/w elevated inflammatory markers (CRP 185, WCC 13.1, Neut 10.86); low Hb 98
- MRI revealed a known pelvic collection and acute sacral osteomyelitis; not for spinal surgery
- Started on 2/7 IV flucloxacillin; 5/7 IV amoxicillin; 26/7 IV pip/taz + PO metronidazole based on culture from referring hospital with +ve E. coli (aug R/ taz S/ cip S)
- D/w colorectal MDT; had CT guided drainage; drain sample grew E. coli resistant to pip/taz but radiological findings improved; switched to IV ceftriaxone 2g OD and PO metronidazole 6/52 on OPAT
- Developed neutropenia and leukopenia on day 8; confirmed on blood film; ceftriaxone was stopped the next day
- Management: switched to IV ertapenem within 24 hours; frequent FBC monitoring;
- Investigations: felt well; NEWS 0 throughout; no new medications; lateral flow test –ve
- Outcome: No complications; quick recovery upon withdrawal of ceftriaxone; remained well and completed 6/52 IVAB as planned

	3 days pre-treatment (had fluclox, amox, taz)	Day 1 ceftriaxone	Day 8 (neutropenia)	Day 9 (ceftriaxone stopped, switched to ertapenem)	Day 14	Day 21
Neutrophil (2.1-7.4 x 10^9/L):	4.94	5.81	1.22	1.93	2.94	3.28
WCC (4.3-11.2 x 10^9/L):	6.5	7.1	2.6	3.9	4.8	5.2

Case study 3

- 87 year-old Caucasian lady repatriated with T4 T5 spondylodiscitis; FBC unremarkable; previous E. coli bacteraemia
- PMH: Angina, thoracic discitis, HTN, polymyalgia rheumatica, Alzheimer's, b/l cataracts, hypothyroidism, Ca thyroid, thyroidectomy
- Referred to OPAT on day 26 ceftriaxone; added in PO co-trimoxazole on day 27 as MRI showed progression
- D/w spinal team – not for surgery due to severity of dementia and comorbidities
- Developed neutropenia and leukopenia on day 30 of ceftriaxone (day 7 of co-trimoxazole); AKI 1 eGFR 68 (86); raised CRP 117 (54)
- Management and investigations:
  - day 2 neutropenia – haematinics NAD; infection screening NEWS 1 (BP 104/55); looked well; diarrhoea ?CDI – stool sample; hydration
  - day 3 – brought onto A&E but discharged back to CH; switched PO co-trimoxazole to PO ciprofloxacin; c/w IV ceftriaxone
  - day 4 - wheezy and bibasilar crackles; no cough or fever; looked well; Covid –ve; increased obs to 4-hourly in care home
  - day 8 - neutrophils continued to worsen; stopped IV ceftriaxone on Day 37 and micro advised c/w PO ciprofloxacin monotherapy
  - day 9 – SDEC review; d/w haem, start G-CSF until Neut ≥ 1 x 10^9/L or max 7 days; had 2 doses on day 12 and 13 since neutropenia
  - day 13 – neutrophils and WCC normalised; c/w PO ciprofloxacin; SDEC review for rising CRP, CXR, ECG, bloods
  - day 14 – a/w abdo pain, loose stools, LRTI on CXR and prolonged QTc (cipro, memantine, sertraline - stopped all 3). Started Tazocin.
  - day 22 – Responded well to Tazocin; discharged back to care home on fast track care with po Cipro.
- Outcome: probable ceftriaxone induced neutropenia, probable infective cause?

	Prior to repatriation	Day 23 ceftriaxone	Day 30 ceftriaxone and Day 7 co-trimoxazole	Day 32 (switched PO co-trimoxazole to PO ciprofloxacin)	Day 34 ceftriaxone and Day 2 PO cipro	Day 37 (ceftriaxone stopped and c/w PO cipro)	Day 38	Day 39 - (filgrastim missed as left out of fridge)	Day 40 (filgrastim missed as no supply)	Day 41 (filgrastim D1)	Day 42 (filgrastim D2)	Day 43 (a/w SOB, started Taz, stopped PO cipro)	Day 47
Neutrophil (2.1-7.4 x 10^9/L):	NAD	5.3	0.37	0.09	0.12	0.02	0.04	0.1	0.13	0.21	5.59	19.34	5.87
WCC (4.3-11.2 x 10^9/L):	NAD	6.6	2.1	1.9	1.7	1.6	2	2	2.4	2.8	9.4	24	9.2

Lessons learnt

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- Importance of FBC monitoring (weekly bloods), MDT, escalation route and history taking
- Risk factors:
  - Drugs
  - Ethnicity
  - Myeloma/pre-existing haem conditions
  - Vitamin B12/ folate deficiency
  - Autoimmune related
  - Infections
- Dose dependent?
- Onset of neutropenia from d1 ceftriaxone: day 37, day 8 and day 30
- Severity: 2 very severe (agranulocytosis) and 1 mild
- All 3 cases were reversible
- Prompt recognition of neutropenia and timely withdrawal of ceftriaxone suggests faster recovery of Neut
- Resolution time from stopping ceftriaxone: 5 days; one case requiring G-CSF
- Two patients remained well, one had LRTI; no known/reported medium- or long-term complications so far
- All three cases subsequently received other beta-lactam antibiotics without developing neutropenia

An ANC <1500/microlitre or <1.5 x 10^9/L is defined as neutropenia and graded as follows:

- Mild: 1000 to 1500/microlitre or 1 to 1.5 x 10^9/L
- Moderate: 500 to 999/microlitre or 0.5 to 0.99 x 10^9/L
- Severe: 200 to 499/microlitre or 0.2 to 0.49 x 10^9/L
- Very severe: <200/microlitre or <0.2 x 10^9/L.

(BMJ, 2022)

Pharmacovigilance and medication safety

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- We also identified cases of:
  - ceftriaxone induced deranged LFTs and thrombocytopenia
- Yellow card reporting
- Safety surveillance – Datix
- Case studies
- Literature monitoring
- Network and sharing best practice

Literature search

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Duncan et al. (2010):

- A case study on ceftriaxone induced severe agranulocytosis and neutropenia in a female in her mid-30s receiving 2g OD on OPAT to treat Lyme disease.

Munir et al. (2022):

- A case study on ceftriaxone induced reversible agranulocytosis in a 78 year-old Caucasian male receiving 2g OD in an outpatient setting to treat infective endocarditis.

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Thank you.

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