OPAT
Outpatient Parenteral Antimicrobial Therapy

BSAC The British Society for Antimicrobial Chemotherapy

Drug Stability : Update and future plans.

Objective Five

To extend the range of anti-infectives and devices available for use within the OPAT patient pathway through publication of standardised open access data.

DRUG STABILITY

BSAC ANTIMICROBIAL DRUG STABILITY PROGRAMME

Tim Hills
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On behalf of the BSAC Working Party on Drug Stability

BSAC Drug Stability Workstream

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Objective Five

To extend the range of anti-infectives and devices available for use within the OPAT patient pathway through publication of standardised open access data.

- Update of progress so far
- PK/PD considerations
- Flucloxacillin Stability results
- Meropenem Stability results
- Clinical experience of buffered continuous infusions

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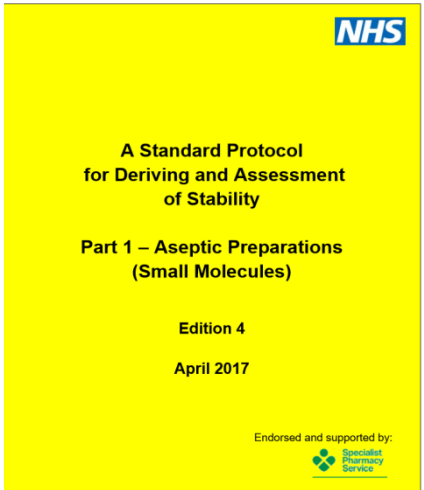
2016 and before

- National OPAT survey
  - Lack of availability of infusion devices was limiting OPAT and effective antimicrobial stewardship in OPAT
- Literature review 121 articles vs NHS QC standards "Yellow Covered Document"
  - No study fully compliant

Jenkins et al JAC 2017



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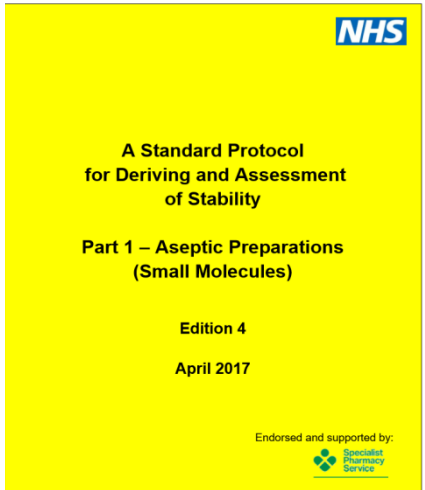
- BSAC- supported programme with industry partners
- Independently verified
- Open-access drug-stability data
- Increasing the opportunity and availability for sterile production for use in OPAT services
- Stability tender awarded
  - Continuous infusion flucloxacillin
  - Continuous infusion meropenem



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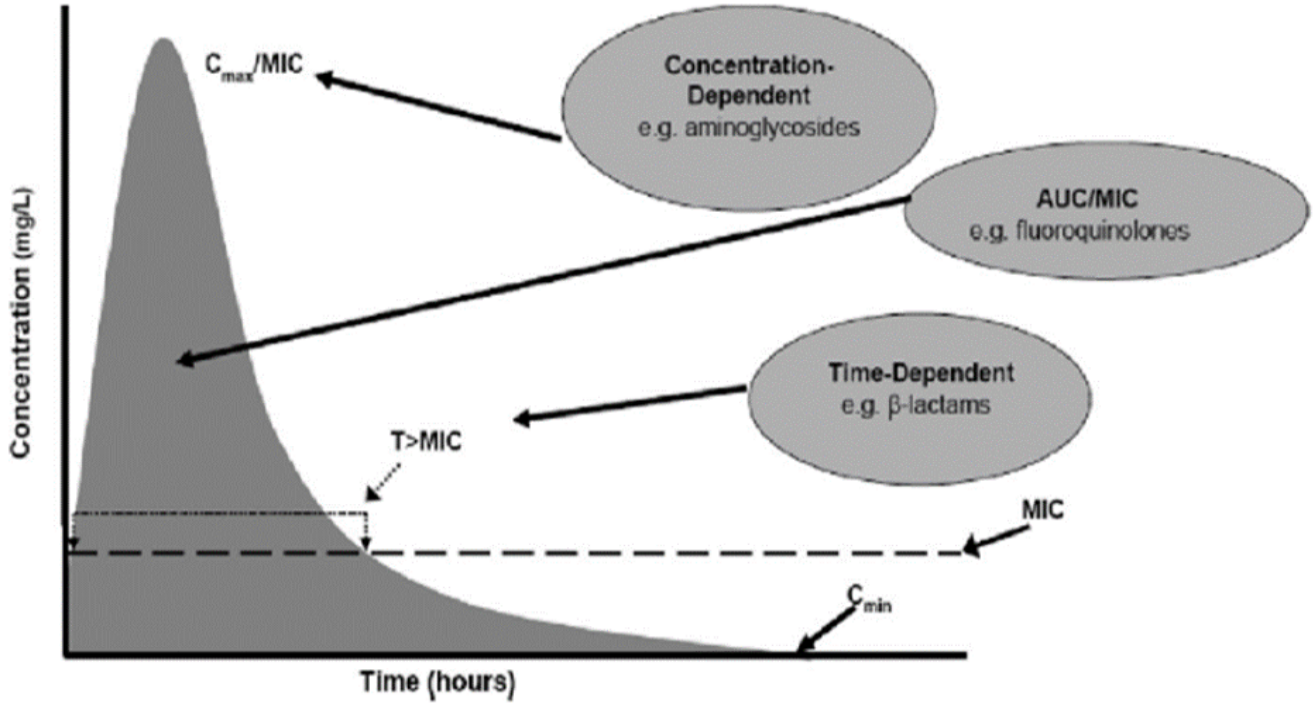
PK/PD consideration



CritCareMed2009Vol.37,No.3

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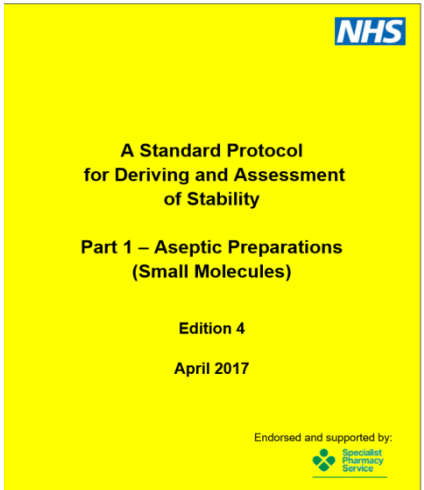
Pre-Scoping Study

- Assessing potentially stable concentration/formulations
- Lower standard of scrutiny

Main Study (YCD)

- Triplicate testing
- Body-worn 32°C
- Two elastomeric pumps
- Shelf-life assignment requires 95-105% concentration (90-105% if degradation products fully understood)



Flucloxacillin - Results

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Pre-Scoping Study

- 10 and 50mg/ml
- Unbuffered➔ unstable at 24 hr
- Sodium citrate buffer 0.3% pH circa. 7

Sodium Citrate 0.3% Buffered Flucloxacillin

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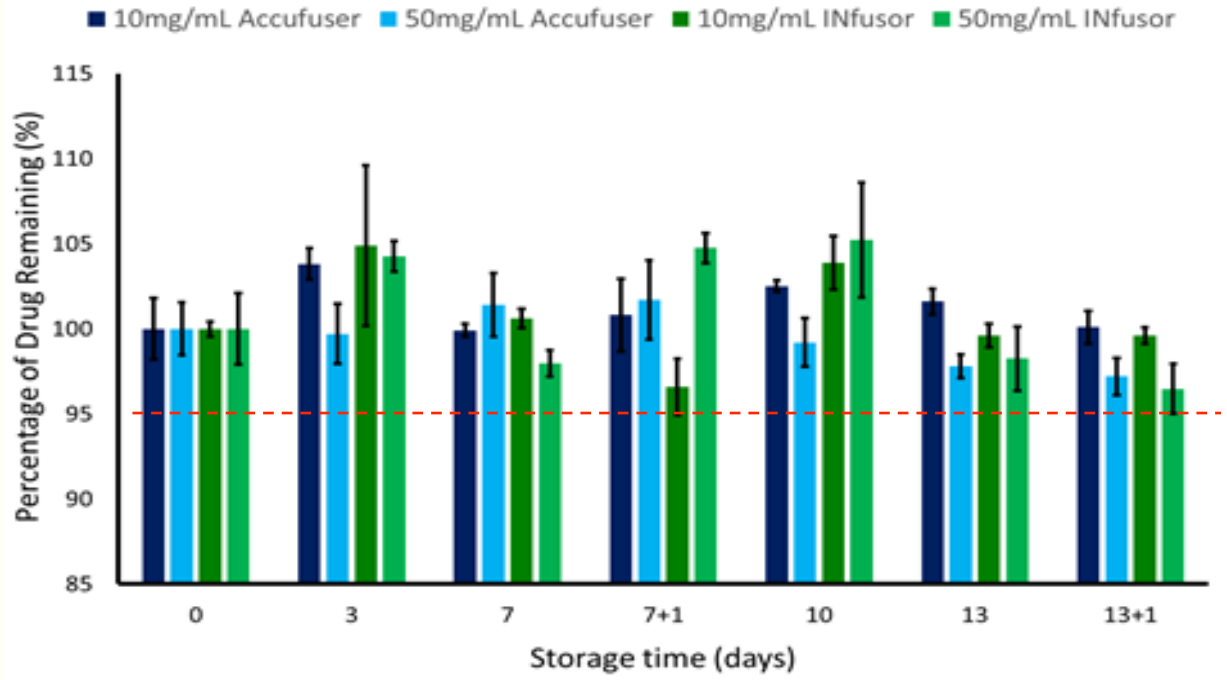
Main Study (YCD)



- Assigned shelf life 13 days 2-8°C then 24 hours at 32°C

Poster: Hills, Allwood et al BSAC OPAT 2017

Pre-Scoping Study

Meropenem – 6.25mg/ml

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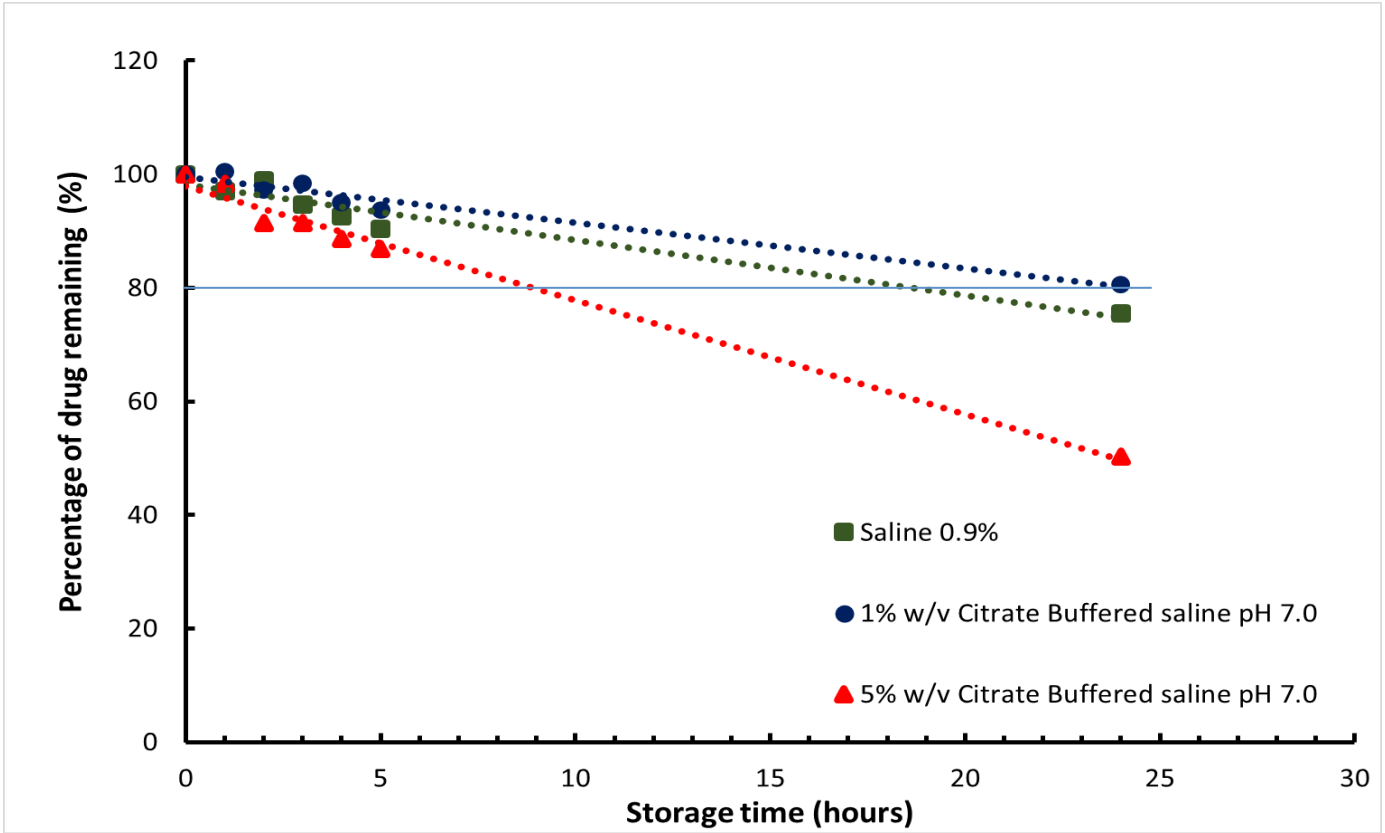

Poster: Hills, Allwood et al BSAC OPAT 2017

Pre-Scoping Study

Meropenem – 25mg/ml

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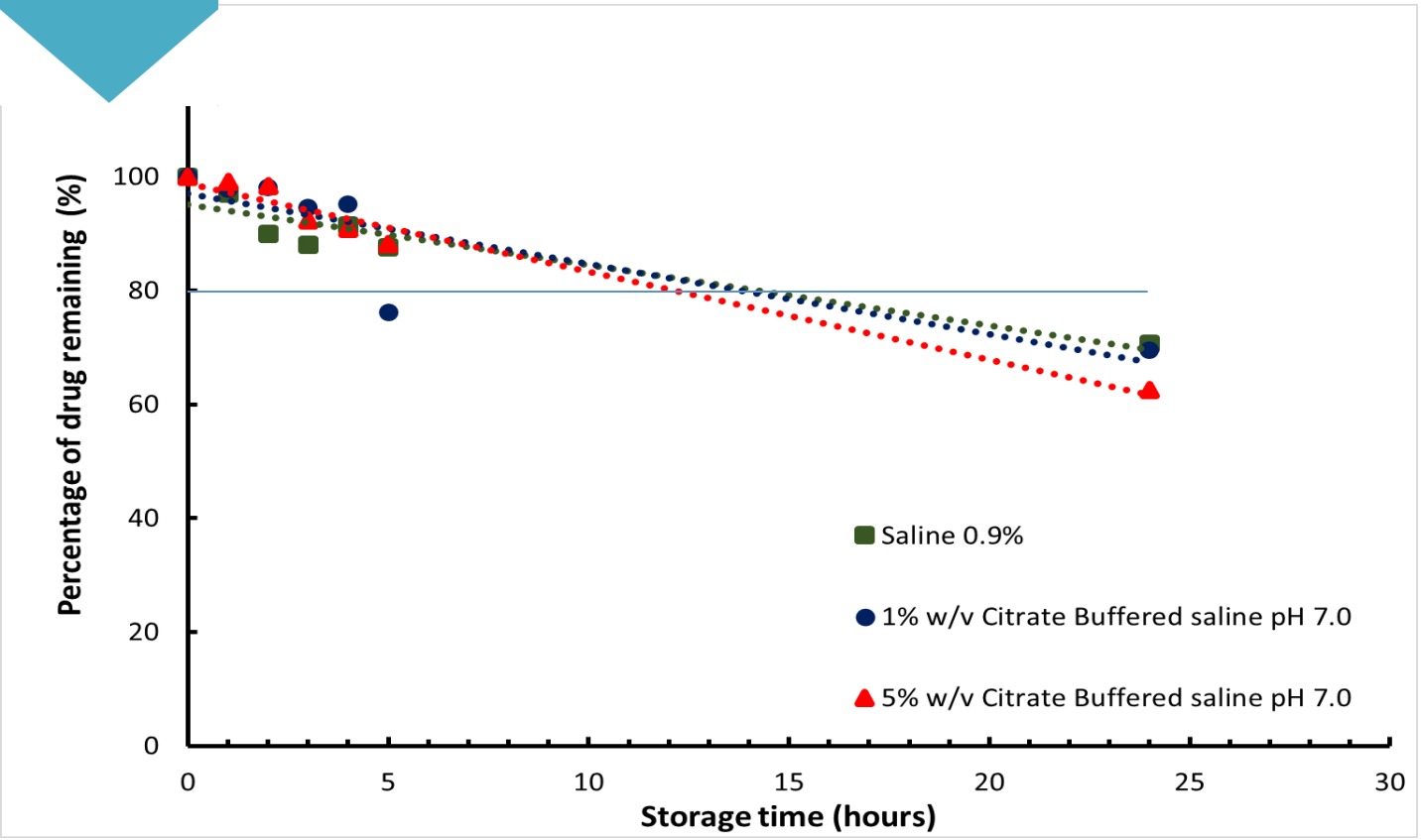
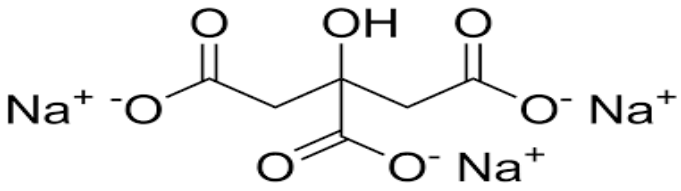
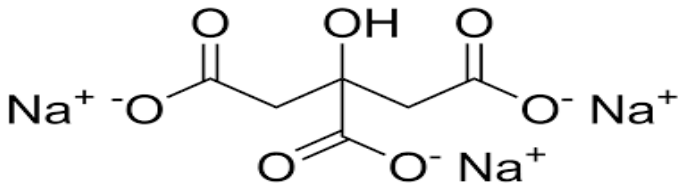
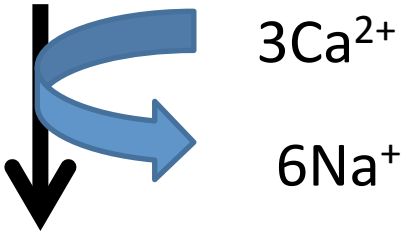


Poster: Hills, Allwood et al BSAC OPAT 2017

Citrate Buffer

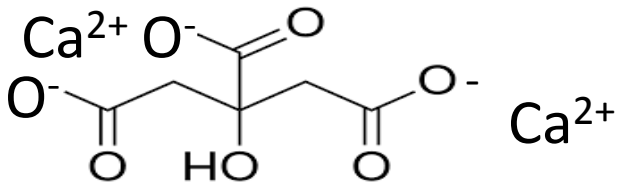




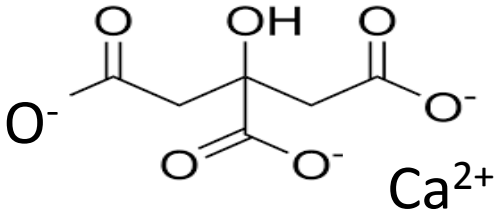


$3Ca^{2+}$

$6Na^{+}$



Ca^{2+}

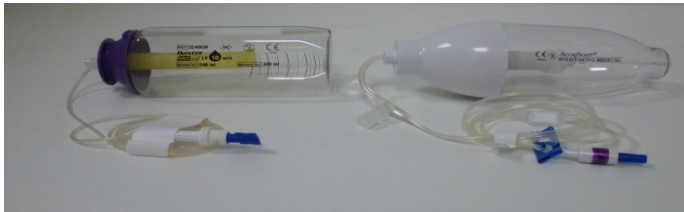


Ca^{2+}

Citrate Buffer – potential issues

	Rationale for measurement
Sodium	To ensure the kidneys are able to manage the additional sodium load
Potassium	Monitoring renal excretion and function
Magnesium	Exclude citrate effect on magnesium
Adjusted Calcium	Trisodium citrate dihydrate buffer may bind to calcium and cause depletion of calcium if the buffer not adequately metabolised by liver
Ionised Calcium	Exclude citrate effect on calcium and to measure any differences in effect on ionised calcium and total calcium for future monitoring plan
Bicarbonate	Effect of citrate metabolism by the liver on bicarbonate concentration
INR	Binding and depletion of calcium may prolong the clotting time

Table 1: Rationale for monitoring bloods in patients receiving citrate-buffered CIV



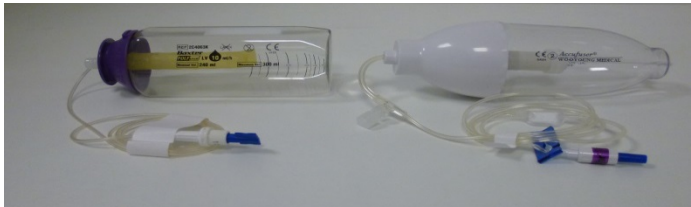
Citrate-Buffered CIV beta-lactams

- 11 patient episodes
  - Fluclox. 8g/24hr (n=4)
  - Fluclox. 12g/12hr (n=2)
  - Pip/taz 13.5g/24hr (n=5)
- A range of infections were treated,
  - Discitis/spinal surgical infection (n=4),
  - Lung abscess/empyema (n=2),
  - Neurosurgical infection, prosthetic joint infection, diabetic foot,osteomyelitis, Enterobacterial pneumonia, bronchiectasis (n=1 each).
- Extended bloods taken at least once

Monitored blood results

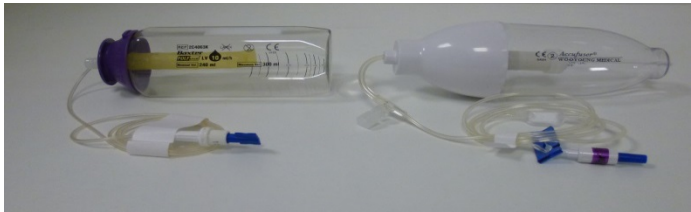
Serum bloods measured	Patients whose levels remained within the normal range on all tests	Patients whose levels fell below the normal range at least once	Patients whose levels rose above the normal range at least once
Sodium	5	3	
Potassium	6	1	1
Magnesium	8		
Adjusted Calcium	6	2	
Ionised Calcium	7	1	
Bicarbonate	4	1	3
INR	8		

- No patient required CIV interruption
- Low Ca^{2+}: 1 x deranged LFTs, 1 x Low Vitamin D
- 9 from 11 “Cured” or “Improved”
- No failures due to buffer



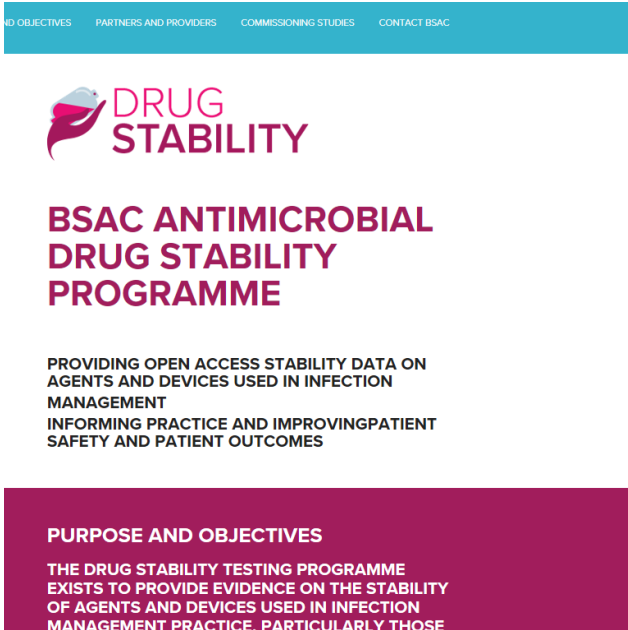
Other CIV issues

- Clamp was not released – missed one day
- Patient cut line whilst gardening
- Line became “stiff” ➔ incomplete infusion
- Drug not running through ?insufficient warm up time or ?patient tampering
- Patient selection important
- Current lead times
- Local preparation



BSAC Drug Stability Testing Programme - 2018

- Publication with open access from http://www.bsac-dsp.com/
- Agents
  - Piperacillin/tazobactam
  - ?Benzylpenicillin
  - Industry partners



Which continuous infusion pipercillin/tazobactam would/do you use in your service?

Voting options for slido

1. 13.5g/24 hour
2. 18g/24 hour
3. Both of the above
4. Either
5. Neither
6. Don’t know/not sure

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2016 and before

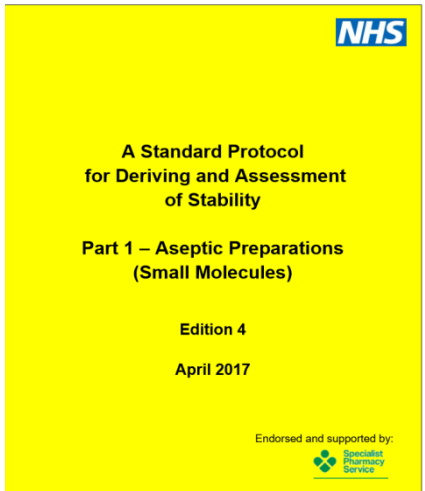
- OPAT survey results
- Literature review vs YCD standards
- Awarding of BSAC tender for Laboratory stability testing in-line with YCD

2017

- Jan- Literature review published JAC
- April - YCD update – 32°C +/- 1°C standard for external body-worn in-use studies
- Results for body-worn CIV flucloxacillin and meropenem
- Piperacillin/tazobactam agreed as next commissioned agent for stability testing

2018

- Publication in peer-reviewed journals as open-access publications, links from drug stability programme website
- Discussions with industry re future testing



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Acknowledgements

- BSAC OPAT Standards Committee - Devices/Drug Stability Work-stream
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