Rapid diagnosis of peritonitis

Martin Wilkie
15 minutes
Disclaimer

• This year, I have received honoraria from Fresenius, Baxter and Triomed.
Problems with the current diagnostic approach for peritonitis

<table>
<thead>
<tr>
<th>Problem</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Presenting features – can be uncertain</td>
<td>eg slightly cloudy bag with no pain, chylous effluent</td>
</tr>
<tr>
<td>Raised effluent white cell count lacks specificity</td>
<td>allergy, malignancy</td>
</tr>
<tr>
<td>Positive culture – lacks sensitivity</td>
<td>Less than 80% sensitive due to culture negative peritonitis</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Lacks sensitivity</td>
</tr>
<tr>
<td>Selecting treatment</td>
<td>Requires to be empirical</td>
</tr>
</tbody>
</table>
Peritoneal fluid cytology (Papanicolaou X600) showing large atypical lymphoid cells - P Viray et al, Perit Dial Int; 2016;36: 350-1.
Patients' Perspectives on the Prevention and Treatment of Peritonitis in Peritoneal Dialysis: A Semi-Structured Interview Study

Campbell D, Perit Dial Int 2016; 36(6):631–639
Ambiguity of Detecting Infection:

• Participants had trouble identifying the first signs of peritonitis and thought instead that they had the flu or that they had gastrointestinal problems. Some experienced only localized pain which they realized later was due to peritonitis.

• One participant recounted that their general practitioner diagnosed a lower bowel infection but did not suspect peritonitis. Women noticed that their bags became cloudy during ovulation.

Campbell D, Perit Dial Int 2016; 36(6):631–639
I was worried the doctor would take my catheter out. I was scared, I thought it would mean I would need an operation. I wasn’t 100% sure if my bag really was cloudy, so I waited until the next day to be sure. I didn’t know who to call at night. I wasn’t sure if I had peritonitis or if something else was wrong. The local hospital weren’t aware that my symptoms could be peritonitis. I felt unwell but waited for Interserve to drain me out. I wasn’t sure if I had peritonitis or if something else was wrong. To presentation………

Laura Gillis, Sheffield.
Exposure to infection

• A doctor could’ve even infected me, didn’t even wash his hands, and I saw how he changed me. (Female, 40s, HD, CAPD and APD)

Campbell D, Perit Dial Int 2016; 36(6):631–639

Why might rapid diagnosis be attractive?

• Quicker access to treatment might lead to better outcomes – eg cure, technique survival, hospitalisation

• The potential to improve quality – for example lower culture negative rates

• Improve our ability to use directed antibiotics reducing pressure on antibiotics, cost and treatment side-effects

• Improve patient confidence in PD and reduce anxiety
Point of care testing is widely used in clinical medicine

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001306
A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis, including:

- leukocyte esterase reagent strips,
- biomarker assays (matrix metalloproteinase-8 and -9, neutrophil gelatinase-associated lipocalin and procalcitonin),
- polymerase chain reaction (PCR) for bacterial-derived DNA fragments,
- 16S rRNA gene sequencing,
- matrix-assisted laser desorption ionization-time of flight (MALDI-TOF),
- pathogen-specific “immune fingerprints” (215–226).
The problem ......
Intra-peritoneal IL-6 signalling in incident PD patients.

Figure 1 — White blood cell count in peritoneal effluent

Figure 2 — Appearance rate of interleukin 6 (IL-6) in peritoneal effluent

Opatrna S et al Perit Dial Int 2012; 32(1):37-44
Distribution of disease and not disease with diagnostic cut-offs and subsequent effects on sensitivity and specificity

https://step1.medbullets.com/stats/101006/2x2-tables-sn-sp-ppv-npv-or-rr
Point of care tests for PD peritonitis in development
MMP-8 and IL-6 were both part of the molecular fingerprint array (of 50 different biomarkers). As a pair on their own, they identify all infections, not “pathogen-specific”.
Summary of disease-specific immune fingerprints in patients presenting with acute peritonitis.

PRINCIPLE OF THE ASSAY

PERIPLEX® detects two recognised markers of infection - Interleukin-6 (IL-6) and Matrix Metalloproteinase-8 (MMP-8) - using a multiplexed lateral flow immunoassay system.

https://mologic.co.uk/periplex/
A point of care “early warning system” to diagnose peritoneal infection in PD patients
Clinical Application
Peritoneal Dialysis (PD)

Rationale
• Infection a leading reason for therapy failure & fatal if left untreated
• Device performance maps well onto existing therapy regime

“Current diagnostic results arrive 48-hours too late” Anand Vardhan (MRI)

Current state of play
• Clinical proof of principle confirmed in 2017
• CE-mark clinical trial scheduled for 2019, market launch late 2019
Underlying technology: **Tetrazolium indicator chemistry**

Reduction of dye chemistry by microbial metabolism causes irreversible colour-change

Application to PD: **Replacement for existing sample bag**

Different ‘channels’ indicate the Gram status of the infection and help guide antibiotic choice

Colour changes signal infection
Validation testing: Manchester Royal Infirmary (MRI)

Effluent sample brought to clinic: is this obviously cloudy?

Unambiguous colour-change from straw colour to deep purple, rather than subjective assessment of cloudiness

Device schematic: Chemistry packaged in pharma capsules

Chambers fill during normal PD effluent drain, dissolving a reporter chemistry contained in soluble pharmaceutical capsules & starting test reaction

Standard Luer lock compatible with existing PD tube sets
Product design
Patient input key to device format & design

Feedback included:
- Compatibility / incompatibility with existing daily therapy regimens.
- Convenience for storage (space requirements).
- Ergonomics / handling and overall ‘design feel’.
- Ease of viewing and interpreting results.
# Example results from preliminary clinical tests

<table>
<thead>
<tr>
<th>Clinical sample</th>
<th>Readout</th>
<th>Result</th>
<th>Information for Doctor</th>
</tr>
</thead>
</table>
| ![Image](image1.png) | ![Image](image2.png) | **G +ve** | Potential source: Touch contamination  
Action: Re-train patient  
Outcome: Prevent re-infection |
| ![Image](image3.png) | ![Image](image4.png) | **G -ve** | Potential source: Bowel  
Action: Treatment & further investigation  
Outcome: Prevent catheter removal? |
| ![Image](image5.png) | ![Image](image6.png) | **WBCs** | Potential source: Early response to infection  
Action: Close obs & possible treatment  
Outcome: Prevention of complications |
Clinical Trial aims

1. Investigate background levels of bacterial infection in non-symptomatic patients.
2. Establish timelines and pathways to presentation with infective peritonitis.
3. Correlate PD device results with conventional hospital microbiology analysis.
4. Investigate if non-culturable infections can be diagnosed effectively?
5. Determine if PD device can be used to diagnose infections earlier than is currently possible.
Point of care (POC) testing

- Point of care testing is growing in relevance in clinical medicine.
- New tests have the potential to improve diagnosis of peritonitis – but there is a long way to go.
- The availability of such rapid or simple tests will not guarantee their adoption or scaling. A whole range of regulatory, economic, policy-related issues will need to be tackled first.
- POC technologies comprise a spectrum of technologies (simplest to most sophisticated), users (lay persons to highly trained), and settings (homes, communities, clinics, peripheral laboratories and hospitals.
- A detailed understanding of context will be necessary to plan most appropriate use.

Pai NP et al, PLOS Medicine 9(9): e1001306
Acknowledgments

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