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The impact of Refractory or Recurrent Liver Ascites on Patients and Healthcare systems and the potential for **alfa**pump® therapy in NASH-related Ascites

Key Opinion Leader Webinar with Hugo E. Vargas, M.D. and Grace Knuttinen, M.D., Ph.D.

15 July 2021

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- The **alfa**pump® system has not yet received regulatory approval in the United States and Canada. Any statement in this presentation about safety and efficacy of the **alfa**pump® system does not apply to the United States and Canada. In the United States and Canada, the **alfa**pump® system is currently under clinical investigation (POSEIDON Study) and is being studied in adult patients with refractory or recurrent ascites due to cirrhosis. For more information regarding the POSEIDON clinical study visit www.poseidonstudy.com.
- DSR® therapy is still under development and it should be noted that any statements regarding safety and efficacy arise from ongoing pre-clinical and clinical investigations which have yet to be completed. DSR® therapy is currently not approved for clinical research in the United States or Canada. There is no link between DSR® therapy and ongoing investigations with the **alfa**pump® system in Europe, the United States or Canada.

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Note:

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Agenda and Presenters

09:00 – Ian Crosbie, CEO Sequana Medical

- Welcome and Introduction

09:00 – Testimonial from a patient living with refractory ascites

09:05 – Dr. Hugo Vargas and Dr. Grace Knuttinen, Mayo Clinic

- Ascites Management 2021
- Treatment and Challenges
- **alfa**pump implantation
- POSEIDON study

09:40 – Ian Crosbie, CEO

- Concluding remarks

09:45 – Q&A

Hugo E. Vargas, M.D.

Grace Knuttinen, M.D., Ph.D.

Ian Crosbie, CEO

Gijs Klarenbeek, Senior Medical Advisor

Patient testimonial

- 63-year old patient from Canada

alfapump® System in the treatment of refractory or recurrent ascites

The POSEIDON Study

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Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Phoenix, AZ

Ascites Management 2021

Objectives

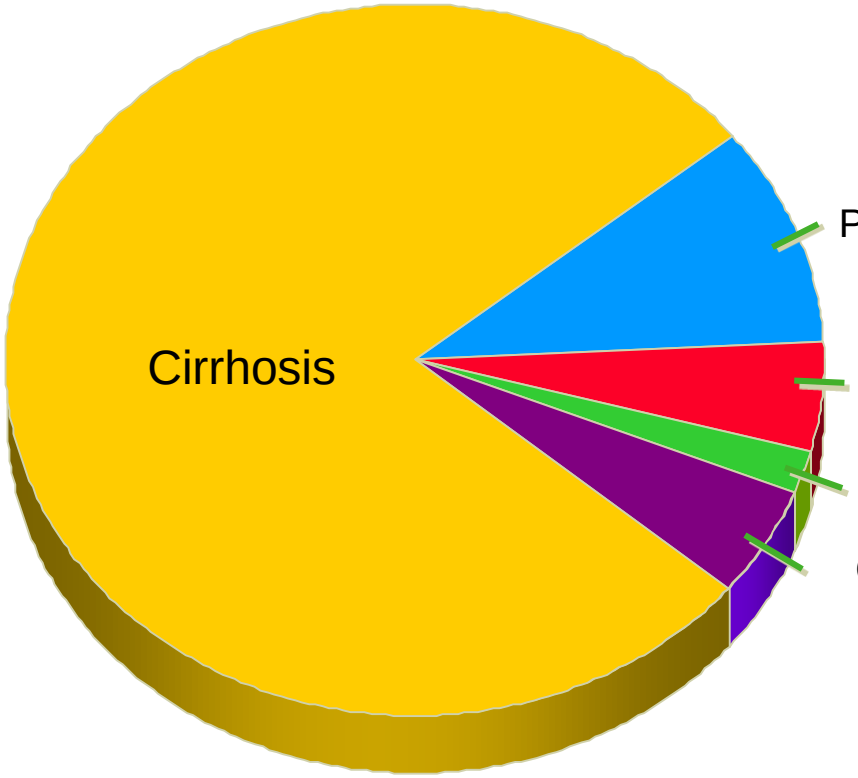
- During this presentation we will discuss:
  - The importance of ascites
  - Clinical implications:
    - *Intensity of clinical burden*
    - *Pitfalls and complications of ascites*
    - *The progress with **alfa**pump*
  - Opportunities and barriers of **alfa**pump

Ascites

- Most common complication of decompensation in cirrhosis
  - Develops in 5–10% of patients with compensated cirrhosis per year
- Significant impact on patients
  - Impairs patient working and social life
  - Frequently leads to hospitalization
  - Requires chronic treatment
  - Direct cause of further complications
  - **Poor prognosis** (5-year survival, ~30%) Consider referral to Liver Transplant (LT) if appropriate.
- Ascites can vary in its manifestations
  - Ascites is **uncomplicated**, **refractory** or **intractable** associated with impairment of renal function

Cirrhosis is the Most Common Cause of Ascites

Etiology of cirrhosis is shifting towards NASH



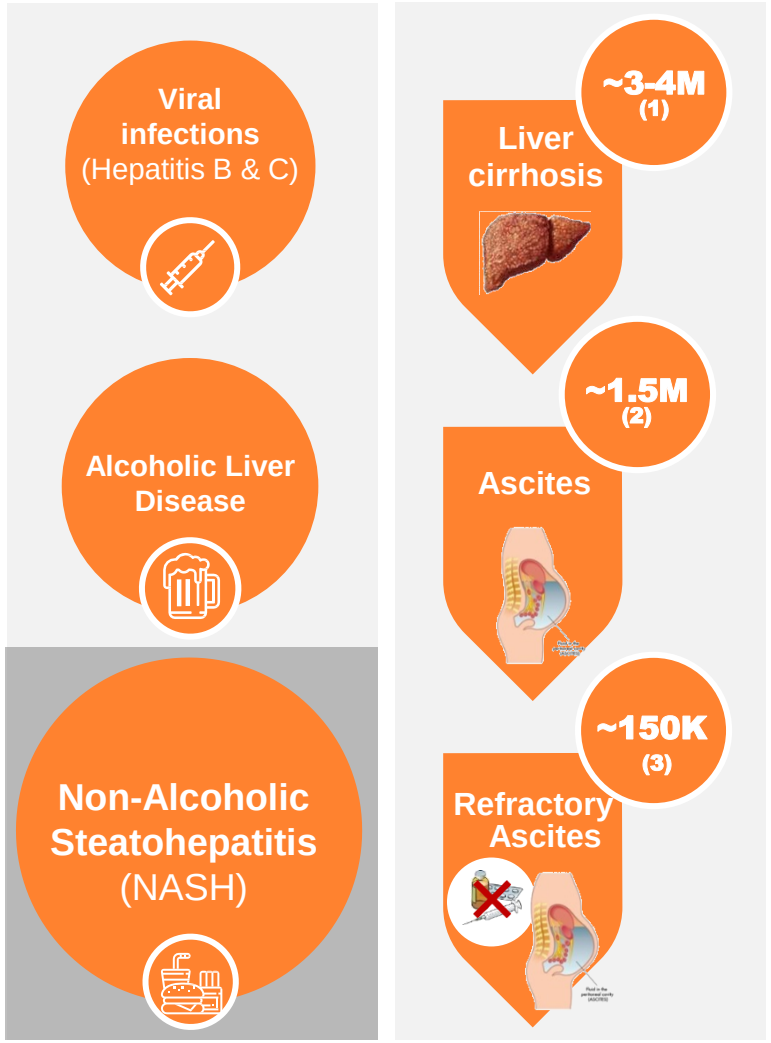
Peritoneal malignancy 10%

Heart failure 3%

Peritoneal tuberculosis 2%

Others
- Pancreatic
- Budd-Chiari syndrome
- Nephrogenic ascites

Prevalence of cirrhosis



Source 1 Management estimate in US based on Estes et al; GlobalData Nash Epidemiology Forecast to 2026; Noureddin et al., 2013
Source 2: Runyon 2009: approximately 50% of cirrhotic patients develop ascites within 10 years of diagnosis of cirrhosis
Source 3: Ginès et al., NEJM 2004: refractory ascites occurs in 5-10% patients with ascites

Ascites Grading

- Diagnostic paracentesis is very important in Grade 2 and 3 ascites (new diagnosis or clinical change)

Grading of ascites*	
Grade 1	**Mild ascites**: only detectable by ultrasound examination
Grade 2	**Moderate ascites**: manifest by moderate symmetrical distension of abdomen
Grade 3	**Large or gross ascites**: provokes marked abdominal distension

Treatment and Challenges

Management of Ascites

- **Grade 1**
  - should alert impending decompensation and management is observant
  - Does not require paracentesis
  - Discuss Na restriction and **follow closely**

- **Grade 2 and 3**
  - Characterize ascites
  - Na restriction (80-120 mmol/day 4-7 g of salt); Dietician directed
  - Therapeutic Paracentesis (Large Volume Paracentesis / LVP) for Grade 3 at presentation
    - **Diuretics**:
      - Key element of initial management

Diuretics

Anti-mineralocorticoid (spironolactone or amiloride)

- **Discontinue for hyperkalemia**

Loop diuretic (furosemide or torsemide)

- **Discontinue for hypokalemia or hyponatremia**

Usual pitfalls:

- Unresponsiveness defines **RESISTANT ASCITES**
  - Be sure maximum doses are used
  - Attempt for at least 1 week
- Complications of diuretics define **INTRACTABLE ASCITES**.
  - Increase in creatinine to >2.0mg/dL, decrease of Na by 10mEq/dL, difficult K management
- **Cramps**: Electrolyte management, muscle relaxants (baclofen, methocarbamol)
- Avoid **NSAIDS, ACE inhibitors and ARBs**
- **Deliberate** about Na restrictions, patients do not always understood by patient.
  - Illustrate and provide handouts, send to dietician
- Check for Na retention by checking urinary sodium

Common Complications

- **Hyponatremia (Serum Na levels below 125 mEq/mL)**
  - Depending on Na level can be serious
  - Required diuretic decrease
- **Spontaneous bacterial peritonitis**
  - Bacterial infection of the ascitic fluid
  - Ambulatory or in-hospital problem
- **Hepatic hydrothorax**
  - Extension of the ascites to the pleural space
  - Requires frequent thoracentesis
  - May be present without ascites
- **Development of acute or chronic complications of kidney dysfunction**
  - May include AKI which can have HRS characteristics, very high mortality

Therapeutic Paracentesis

Any patient with G3 ascites (tense) on appropriate diuretic regimen who is struggling with ascites control

Consider LVP regimen if:

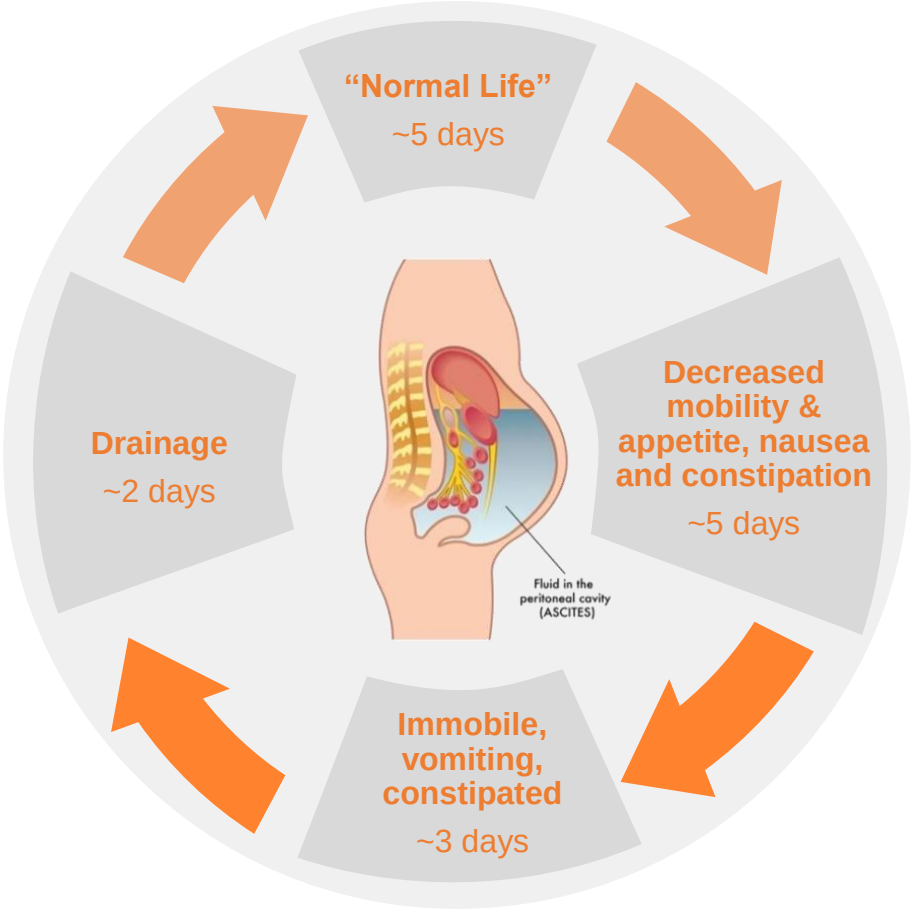
- Ruled out non-compliance with Na restriction
- No response or symptoms with maximal regimen of diuretic combination

Patients benefit from standing order for LVP

- Routine evaluation of cell count and differential
- Need for cultures if addressing **admission-related** LVP
- Albumin replacement using 8g of 25% albumin per liter of ascites drawn. Volumes of less than 5 L may not require albumin if renal function is preserved.
- **Very burdensome for patients as it can be quite frequent**

Refractory/Recurrent Ascites and Paracentesis

Significant impact on Quality of Life



Typical patient life(1)

Note : Prevalence of NASH in US is expected to increase by 63% between 2015-2030; Estes et al., 2018

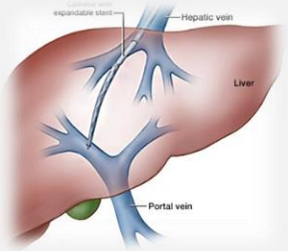
Source 1: Presentation of Dr. Rajiv Jalan at EASL in 2018, Large Volume Paracentesis (LVP) treatment cycle for refractory ascites

Limitations of Existing Therapies

Drainage ("Large Volume Paracentesis / LVP")

Painful, Poor Quality of Life, Short Term Benefit

Transjugular Intrahepatic Portosystemic Shut (TIPS)



Complications, Contraindications

Permanent Catheter System

External Catheter, Risk for Infections / Blockage

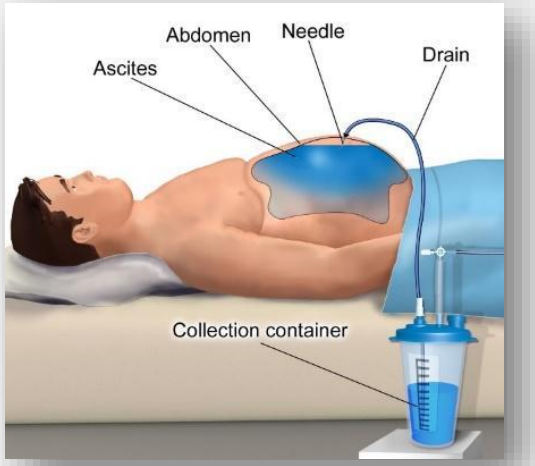
Liver transplantation

High Cost, Limited Availability

alfapump®

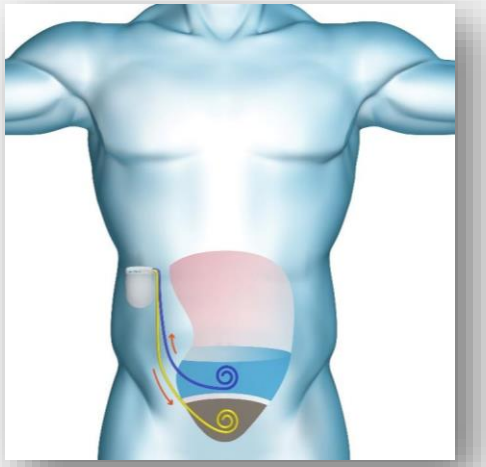
alfapump® – Reduce the Need for Therapeutic Paracentesis

Therapeutic Paracentesis



- Painful
- Frequent hospitalisations
- Poor quality of life
- Short-term benefit

alfapump®

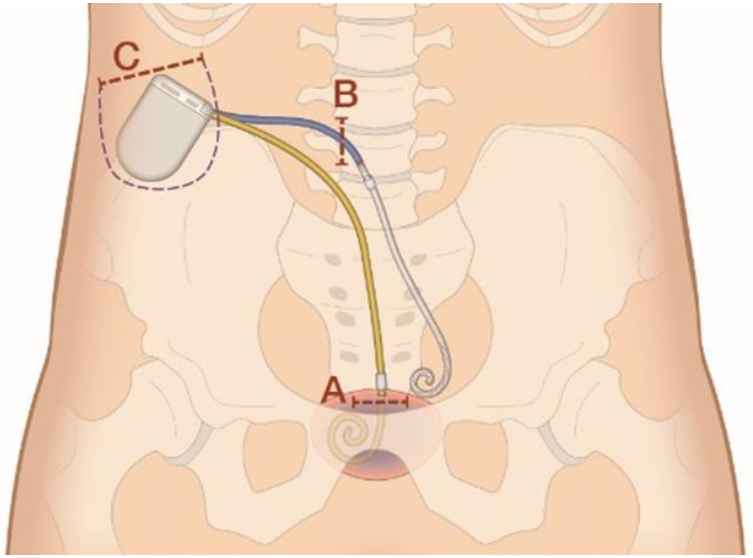


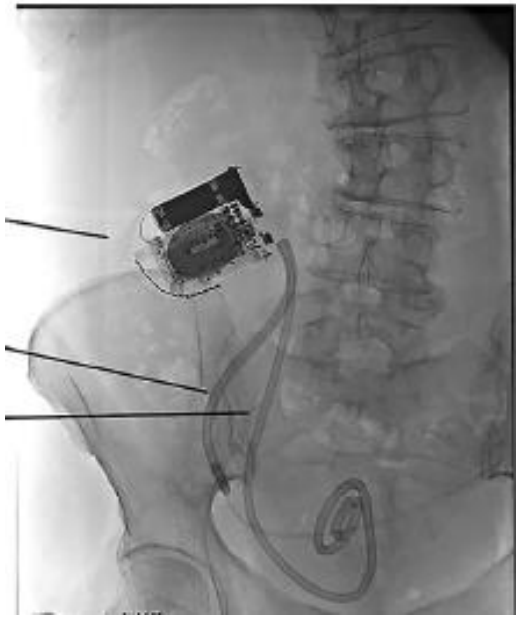
- ✓ Automatic and continuous removal of ascites
- ✓ Fully implanted and wirelessly battery charging
- ✓ FDA breakthrough designation / CE mark
- ✓ Over 850 implants to date

alfapump® Implantation

alfapump® Implantation

- Minimally invasive procedure
  - Takes around 60 minutes
  - Performed by Interventional Radiologist
  - Straightforward procedure using standard techniques
- Performed under general or local anaesthesia
  - In standard treatment room
- Procedure Protocol:
  - Place peritoneal catheter then bladder catheter (1-2 cm incisions)
  - Create standard pump pocket (4 cm incision)
  - Tunnel and connect catheters to **alfa**pump

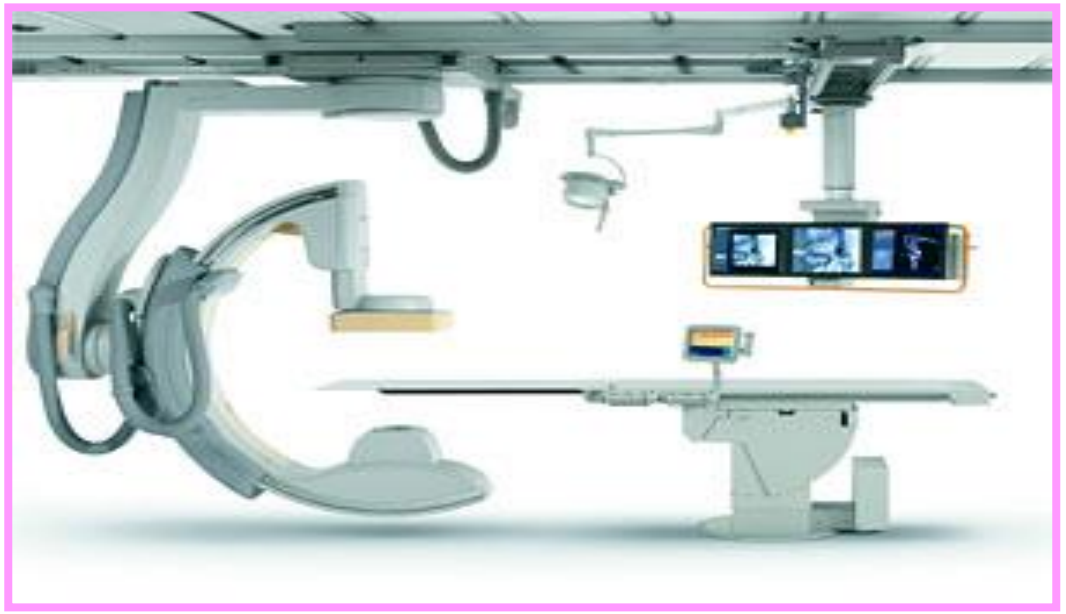




What is an Interventional Radiologist?

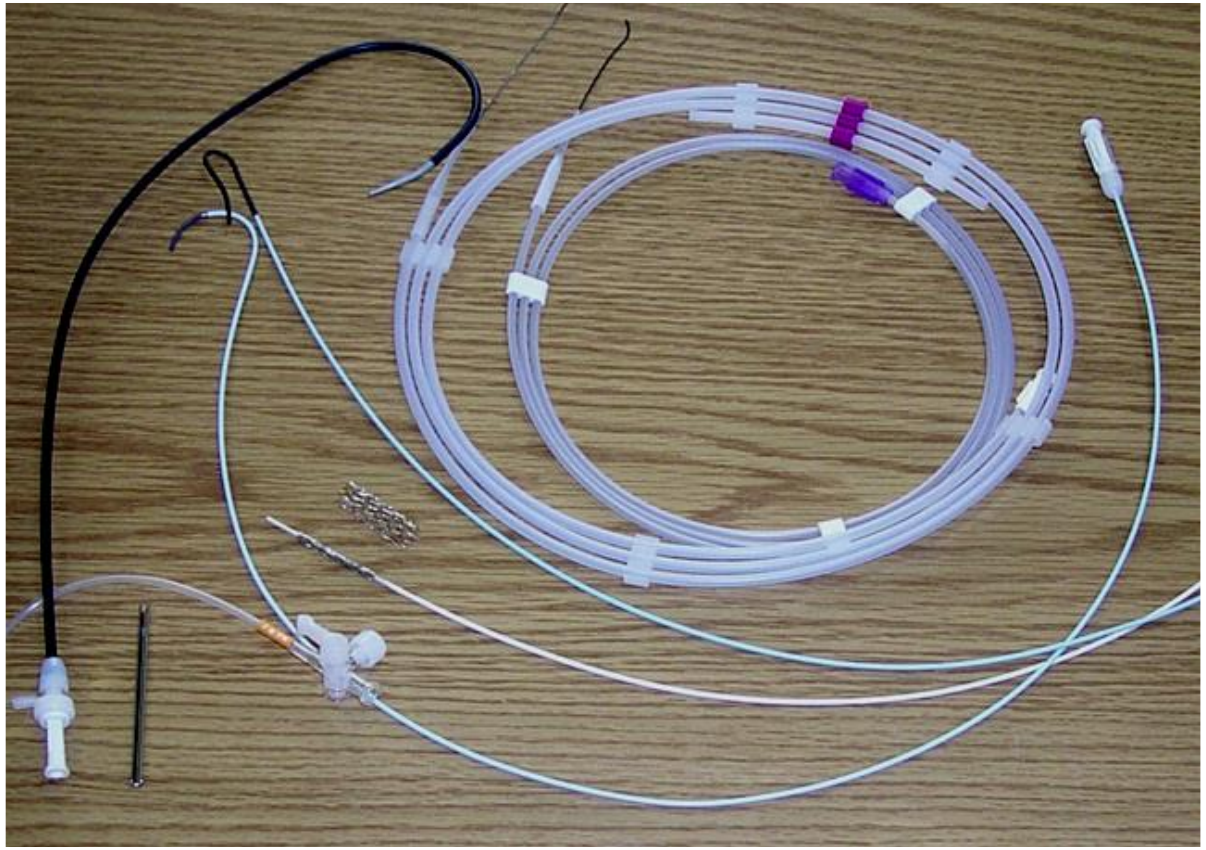
- Interventional radiology treatments are generally easier for the patient than surgery because they involve no surgical incisions, less pain and shorter hospital stays

- Interventional radiologists are physicians who are specially trained to diagnose and treat conditions using tiny, miniaturized tools, while watching their progress on X-ray or other imaging equipment
- Typically, the interventional radiologist performs procedures through a very small nick in the skin, about the size of a pencil tip



What are “Minimally Invasive” Techniques?

- needles
- guide wires
- catheters
- stents

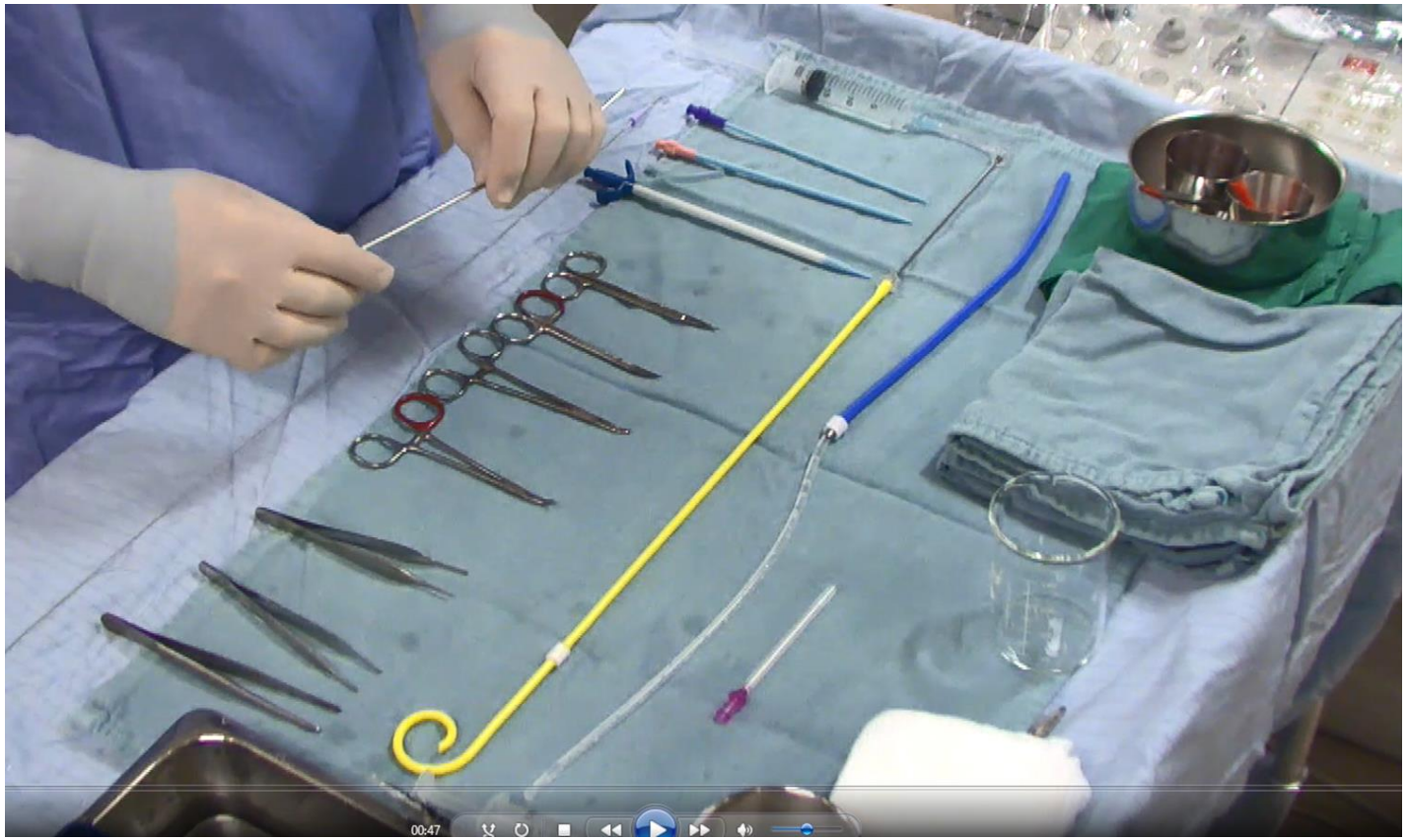


alfapump® IR Implant Procedure

1. Pre-Implant ; Choice of the right patient
2. Anesthesia
3. Implant
    - Peritoneal Catheter
    - Bladder Catheter
    - Pump Pocket and Catheter Tunneling
    - Pump Fixation
    - Pump Volume, Albumin and Infection
4. Post-implant
    - Adjust volume (if required)
    - Out-patient follow-up

What's in the "Box"?

1) PUMP
2) BLADDER CATHETER
3) PERITONEAL CATHETER
4) IMPLANT ACCESSORIES

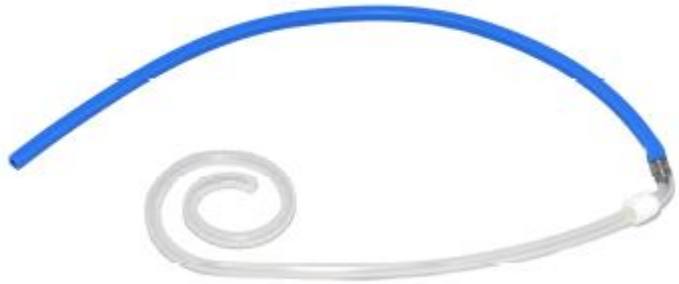


The alfapump® Catheters

- Standard implantable grade silicone catheters are utilised to move ascites from the abdominal cavity to the bladder

YELLOW is BLADDER

- Pigtail to ensure safety and no irritation against the bladder wall

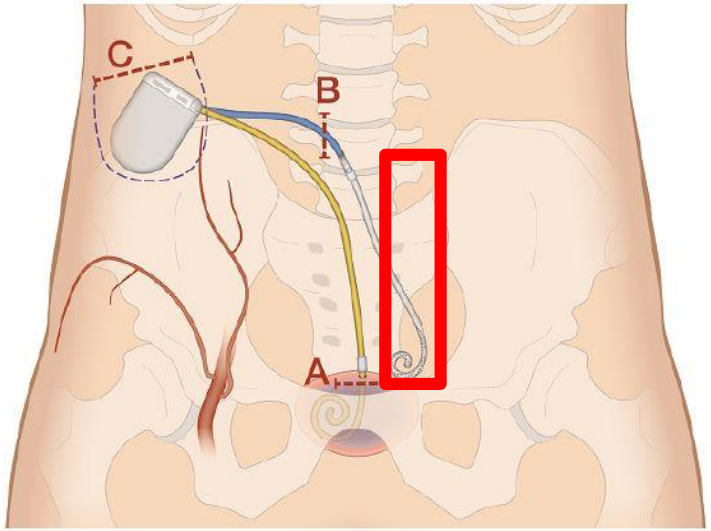


TRANSPARENT / BLUE is PERITONEAL CAVITY

- Pigtail to avoid blockage and intraperitoneal migration

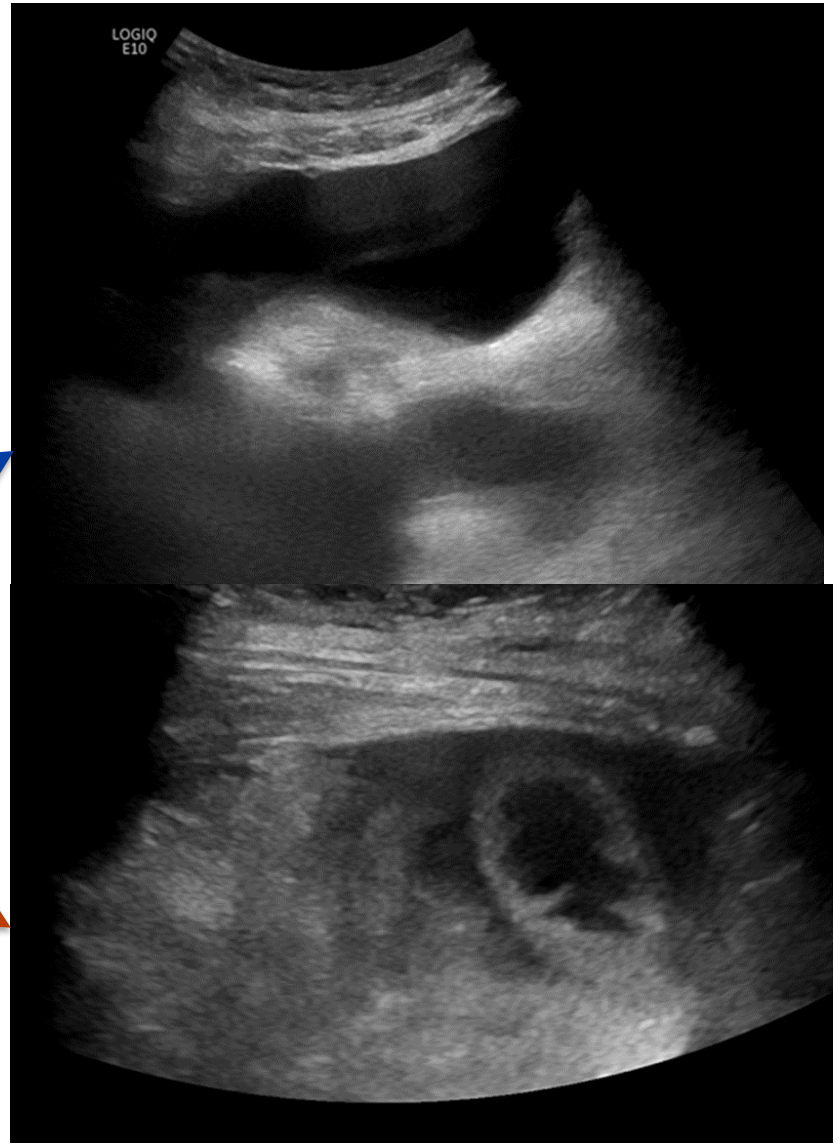
Peritoneal Catheter Placement

- Locate the insertion site
  - Typically near the right pericolic gutter
- Can be individualized to patient anatomy
  - Subcutaneous path of the peritoneal catheter should be at least 10 cm
- **Use Doppler ultrasound to avoid any large vessels**
- Incision site should not sit directly below pressure points
- Create an incision through the skin of approximately 1cm



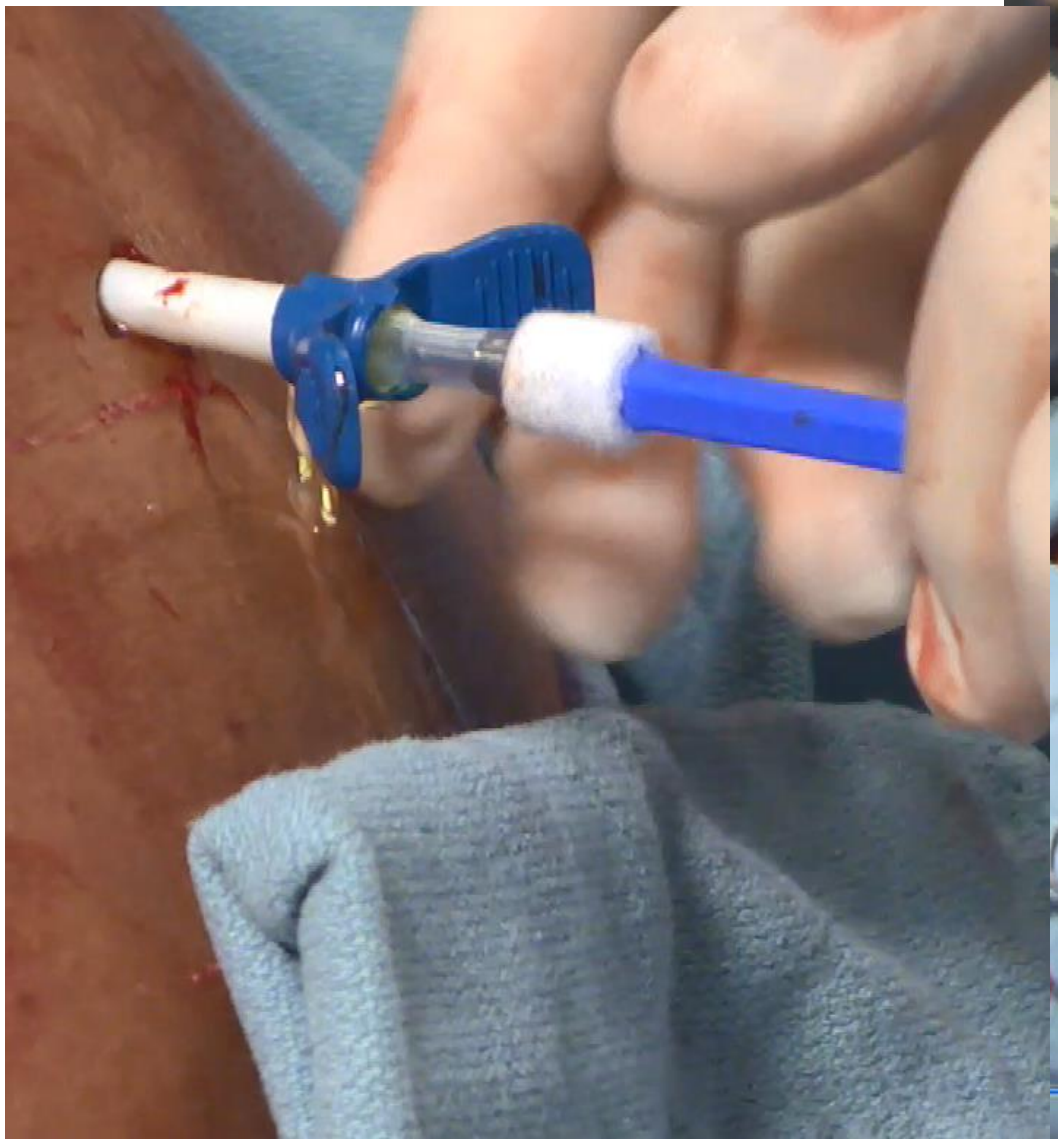
Ultrasound

- To locate optimal abdominal entry (ascites) for the peritoneal catheter



Wire, Dilate and Peel Away Sheath

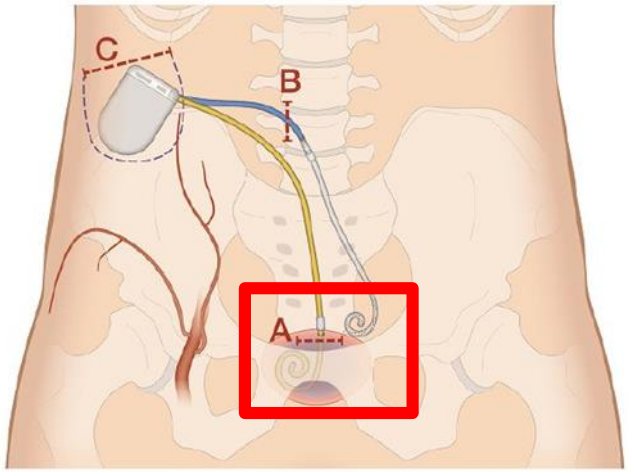
Standard methods for (IR) catheter placement



Bladder Catheter Placement – Suprapubic Approach

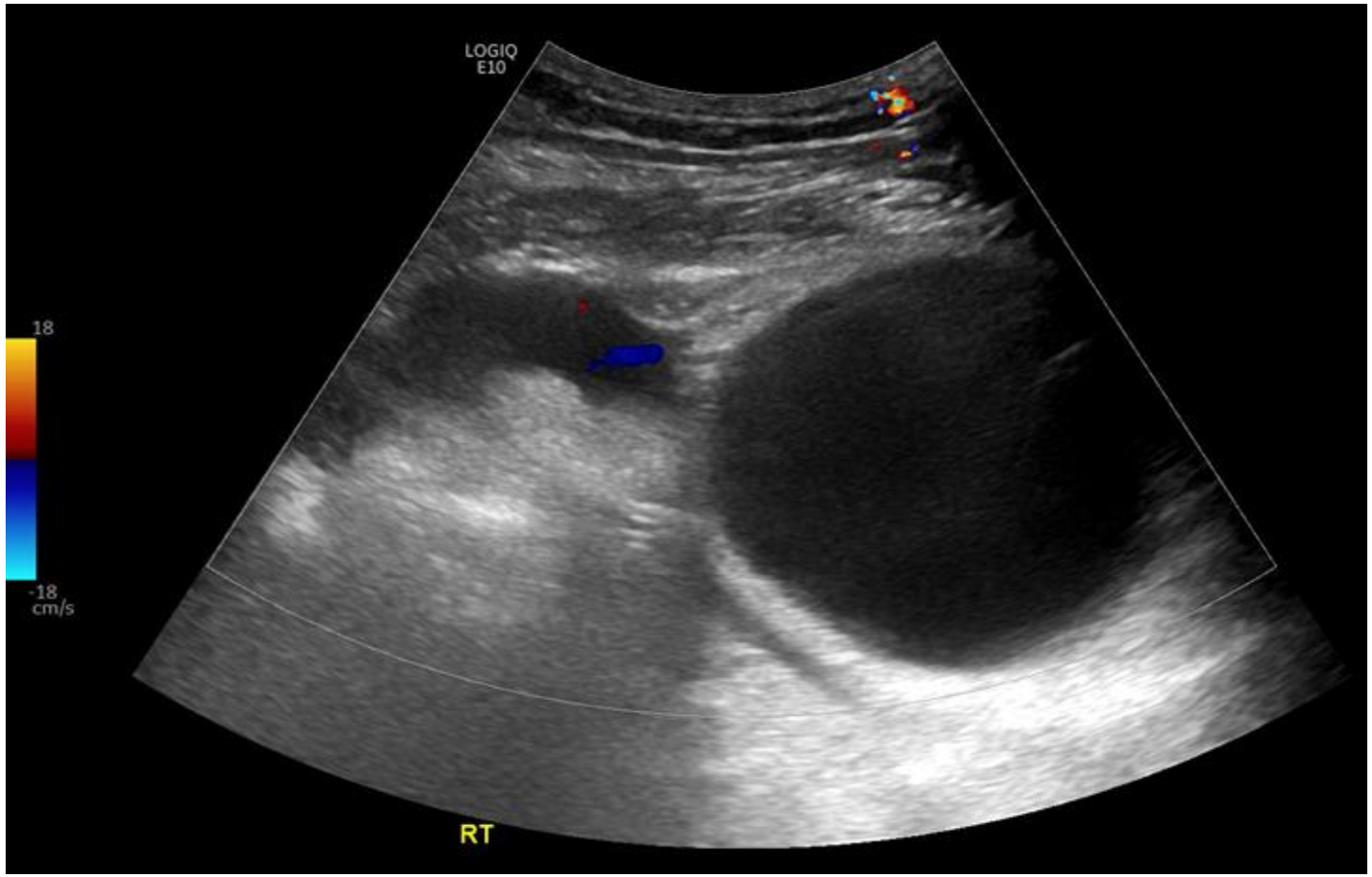
- **Assess the bladder with ultrasound**
- Locate the incision site above the symphysis pubis and below the palpable bladder dome
- Incision site should be right to the midline
- Perform a bladder “stab” with the introducer/needle

  attached to a small syringe while aspirating.
  - Confirm the correct placement by free aspiration of urine/saline
  - **Optional**: check correct location with contrast solution
- Suprapubic approach passes through the tissues of the lower abdominal wall directly into the bladder and should not traverse the peritoneal cavity

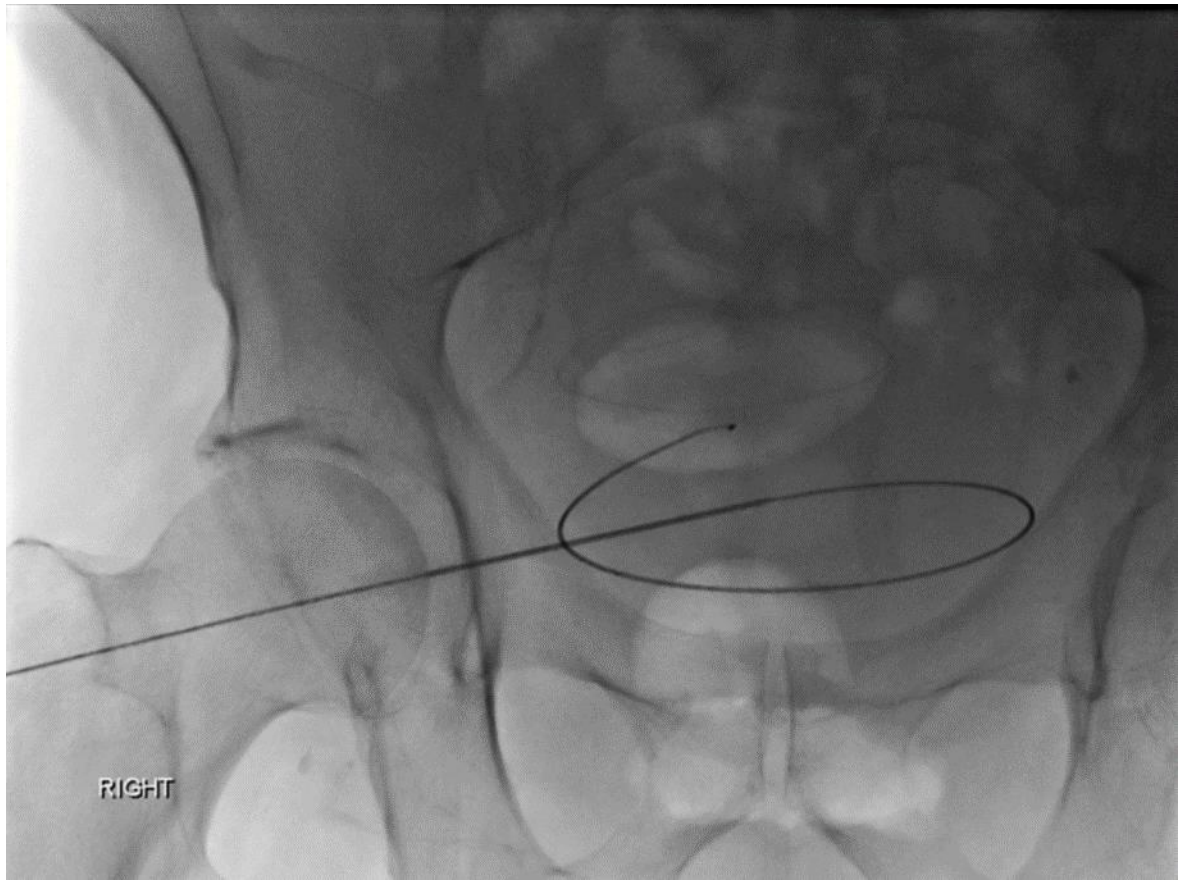


Bladder Ultrasound - Use Doppler!!!

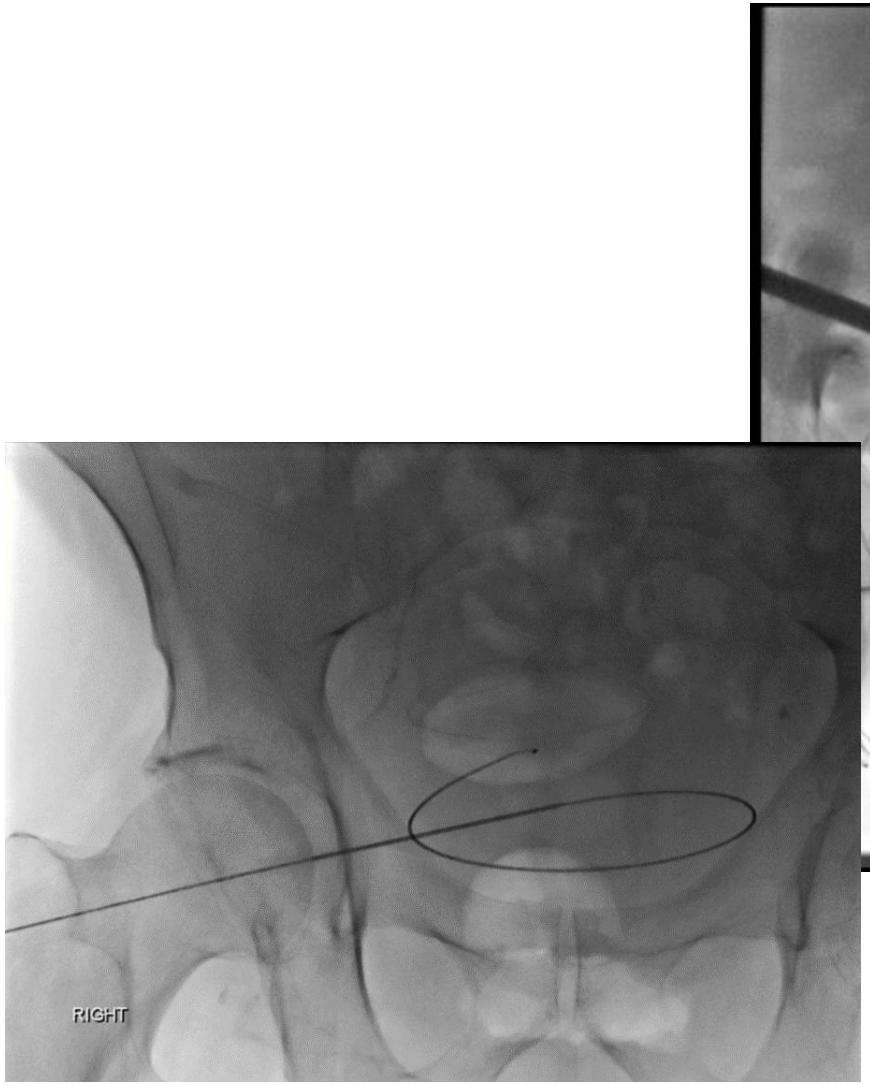
Importance of localization of bladder in patient with ascites: peritoneum can “hang over” the bladder

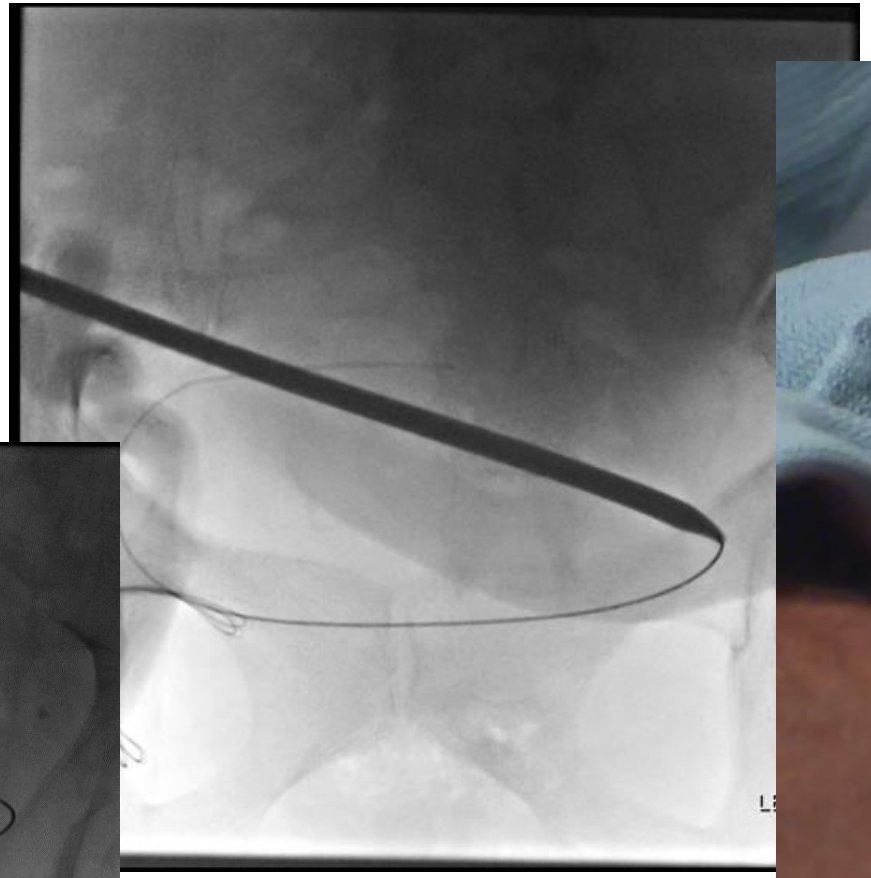


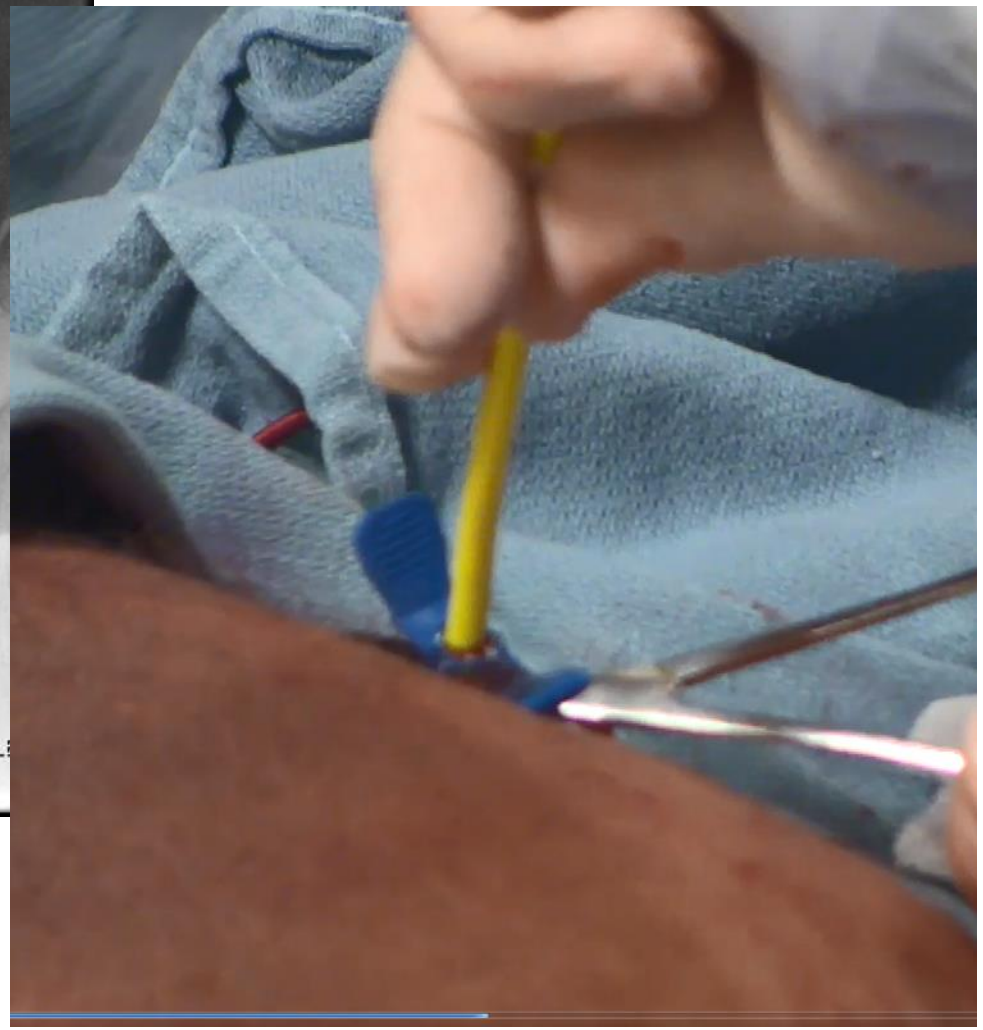
Bladder Catheter Placement



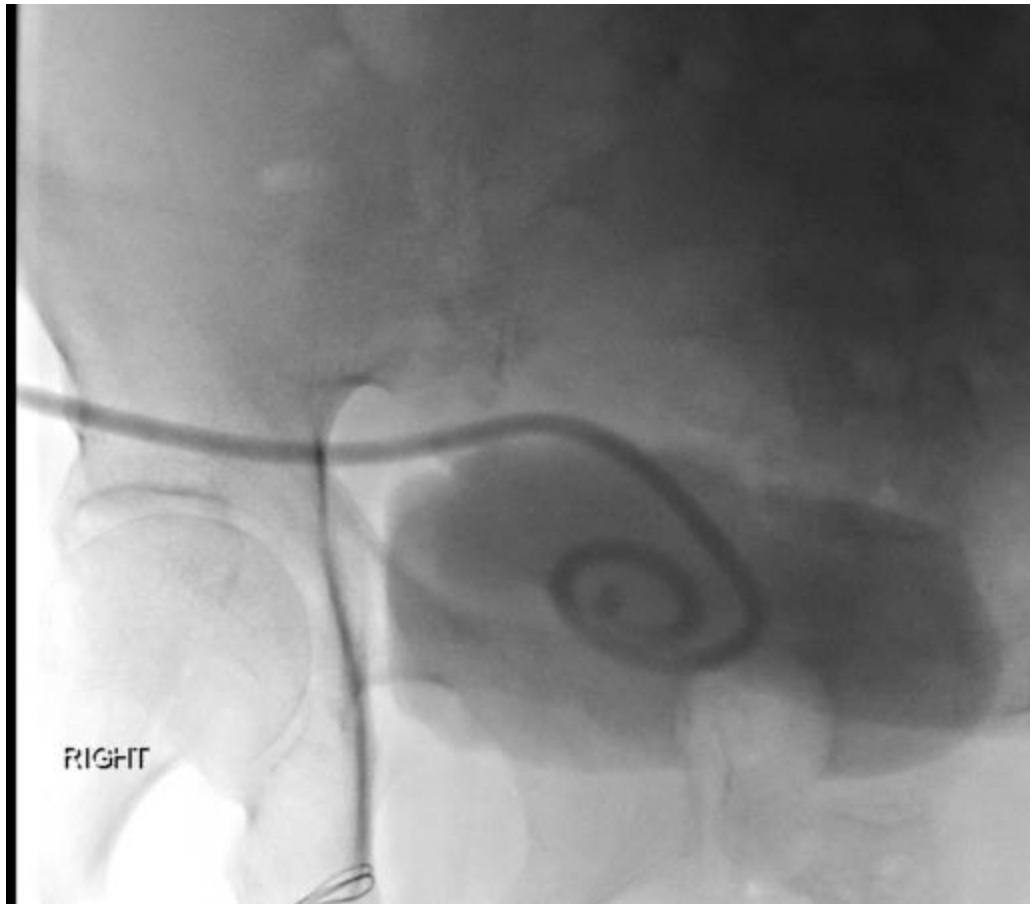
Wire, Dilate and Peel Away Sheath – Similar to PC



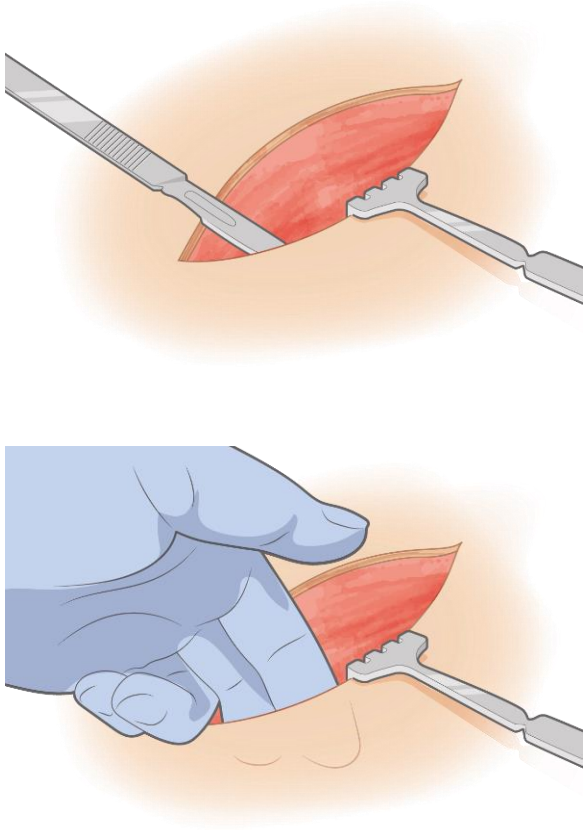


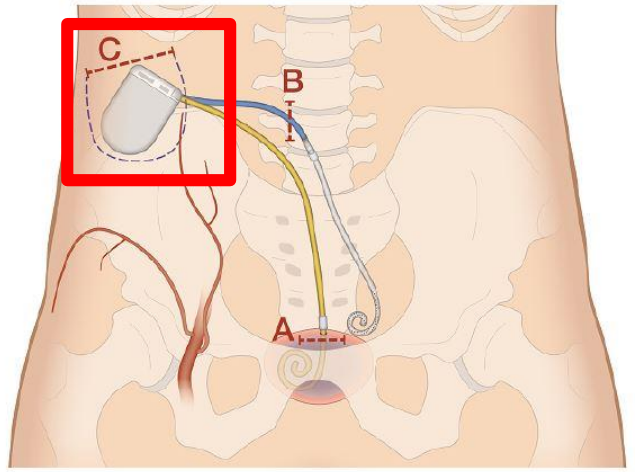


Bladder Catheter Placement

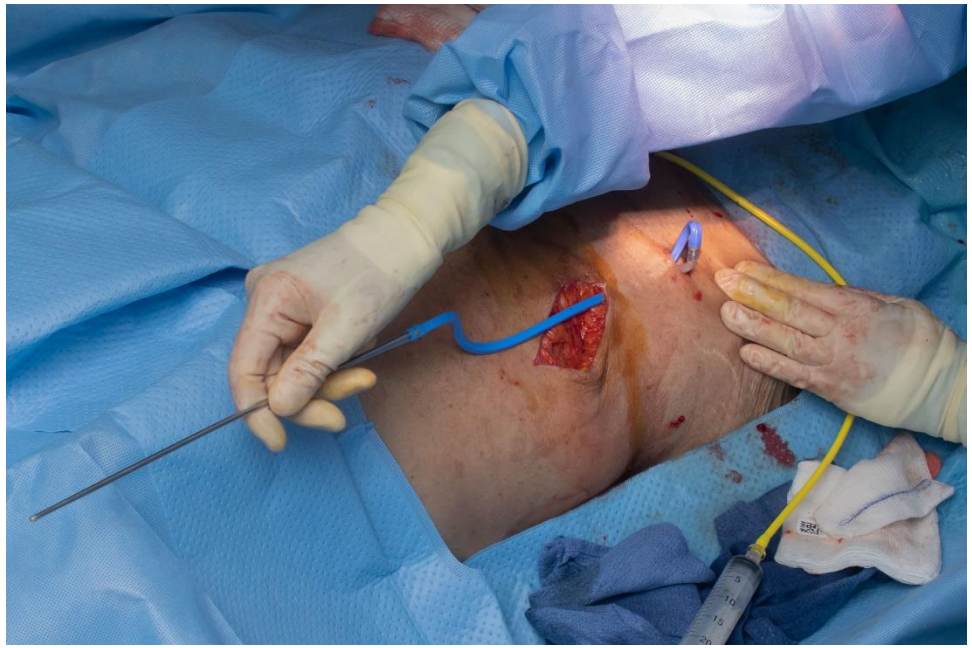


Pump Pocket Creation

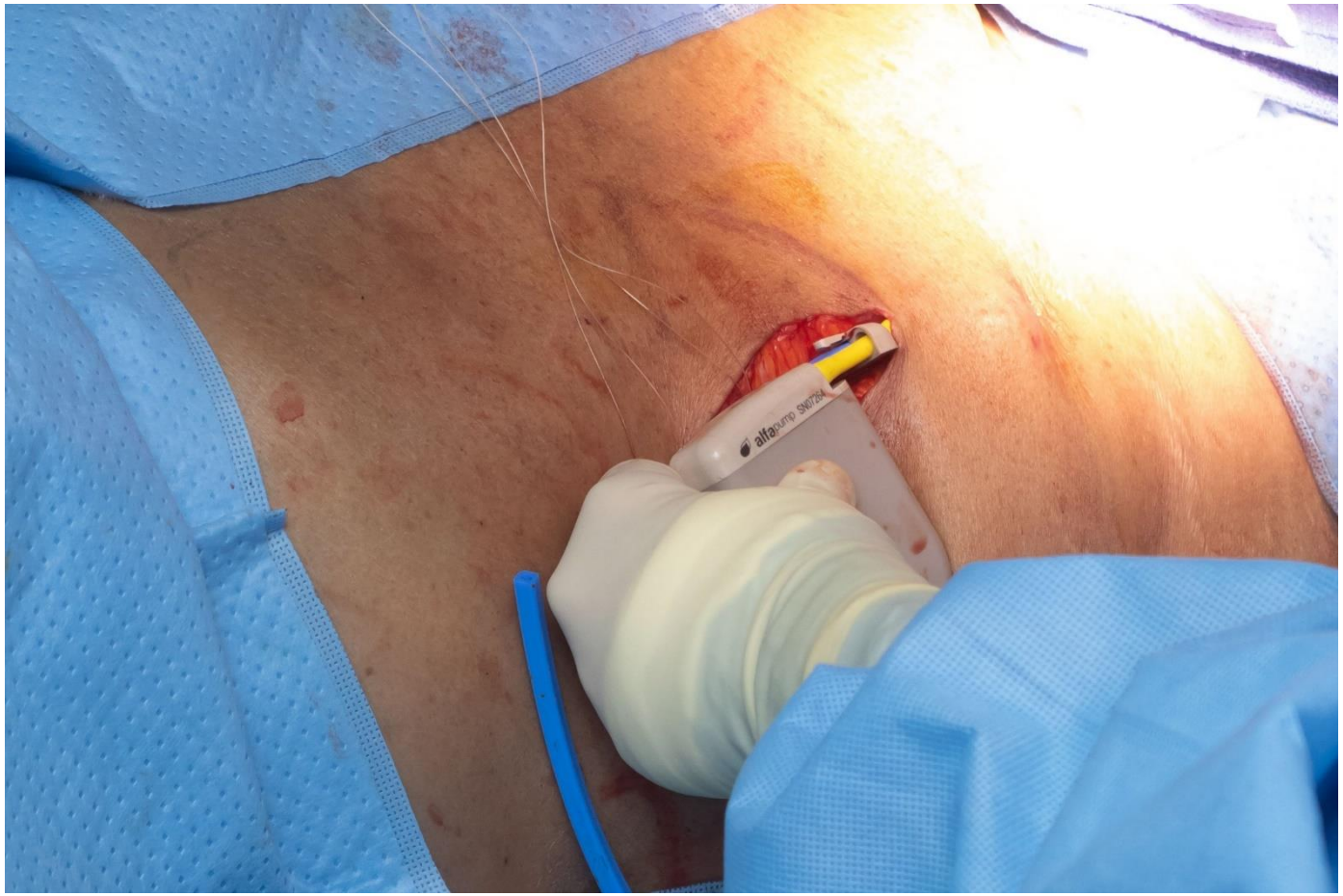




Tunneling of Catheters

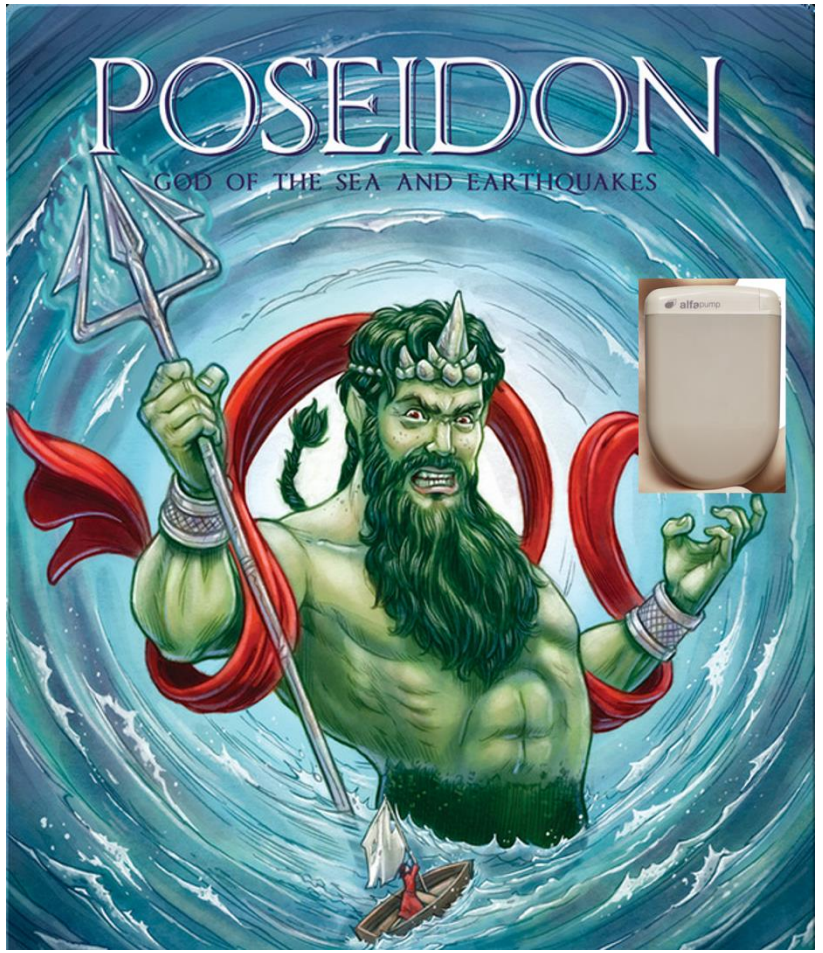


Attach Catheters to alfapump® and Test



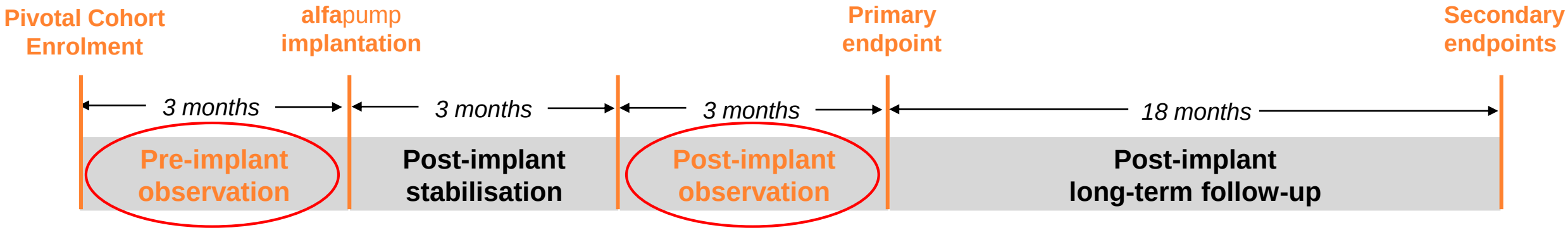
Closing of Incisions

POSEIDON Study



Study Design

Pivotal study to support future marketing application of the alfapump® in the US and Canada



Two study cohorts with the same inclusion / exclusion criteria

- Pivotal Cohort – for primary and secondary endpoint analysis
- Roll-In Cohort – to familiarise new centres with **alfa**pump implantation

Recurrent or Refractory Ascites – Patient Profile

- **26 patients** from the Roll-In Cohort in the POSEIDON study

Age (mean)	63 y
MELD score (mean ± SD)	10.3 ± 3.9
Cirrhosis etiology	
- Alcohol	- 50.0%
- NASH	- 23.1%
- NASH / Alcohol	- 3.8%
- Alcohol / Hepatitis	- 11.5%
- Alcohol / Primary Sclerosing Cholangitis	- 3.8%
- Hepatitis C	- 3.8%
- Budd Chiari Syndrome	- 3.8%
Therapeutic Paracenteses per month prior to study (mean ± SD)	3.8 ± 1.4

MELD: *Model for End-stage Liver Disease;* ***SD:*** *Standard Deviation;* ***NASH:*** *Non-Alcoholic Steatohepatitis;* ***TP:*** *Therapeutic Paracentesis*

Roll-In Cohort: Substantial and Durable Reduction in Therapeutic Paracentesis (TP)

Mean values	Primary efficacy endpoint Pivotal Cohort	Interim data Roll-In Cohort (N = 26)
% reduction in monthly frequency of TP	> 50% (1)	> 90% (2)
% patients with >50% reduction in TP	> 50% (1)	100% (2)

(1) Monthly frequency of TP during 3-month post-implant observation period (month 4 to 6) vs 3-month pre-implant observation period

(2) Monthly frequency of TP during period up to 12 months post-implant vs one month prior to implant (medical history)

Substantial reduction in TP well beyond 6 months post-implantation with alfapump®

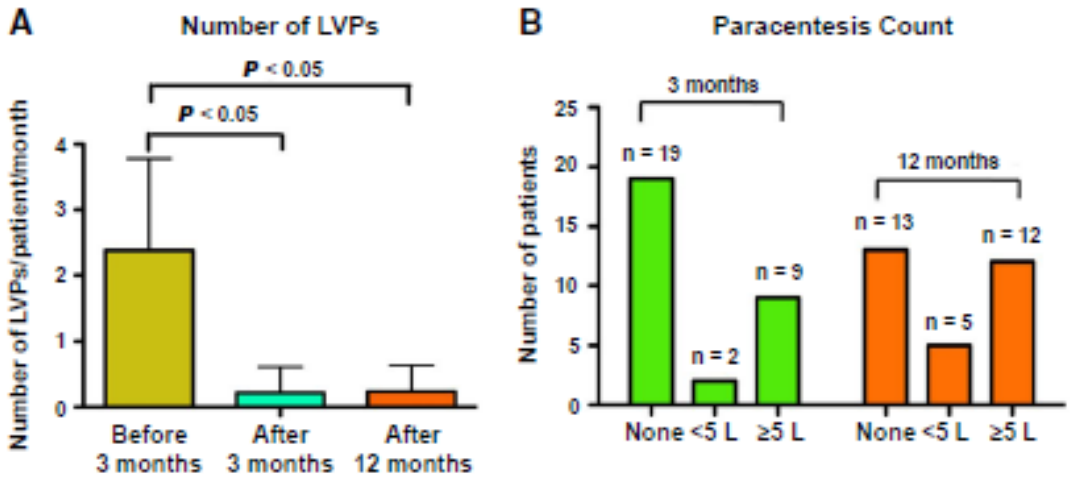
** Note: Pre- and post-implant periods for this analysis of the Roll-In Cohort differ from those that will be used for the Pivotal Cohort analysis*

TP: *Therapeutic Paracentesis*

MOSAIC Trial: a Previous North American Feasibility Study with the alfapump®

Phase II study
Enrolled 30 patients

- Ascites drainage pre-implantation decreased from 2.4 ± 1.4 LVP/patient/month to 0.2±0.4 LVP/patient/month
- Patient QOL and weight improved after implantation



Consistent with the currently presented results

Wong 2020 Liver Transplantation, 26 651

Roll-In Cohort: Safety In-line with Expectations

Primary safety endpoint:

- Rate of **alfa**pump related re-interventions adjudicated by Clinical Events Committee (CEC)

  Interim data Roll-In Cohort (N=26):

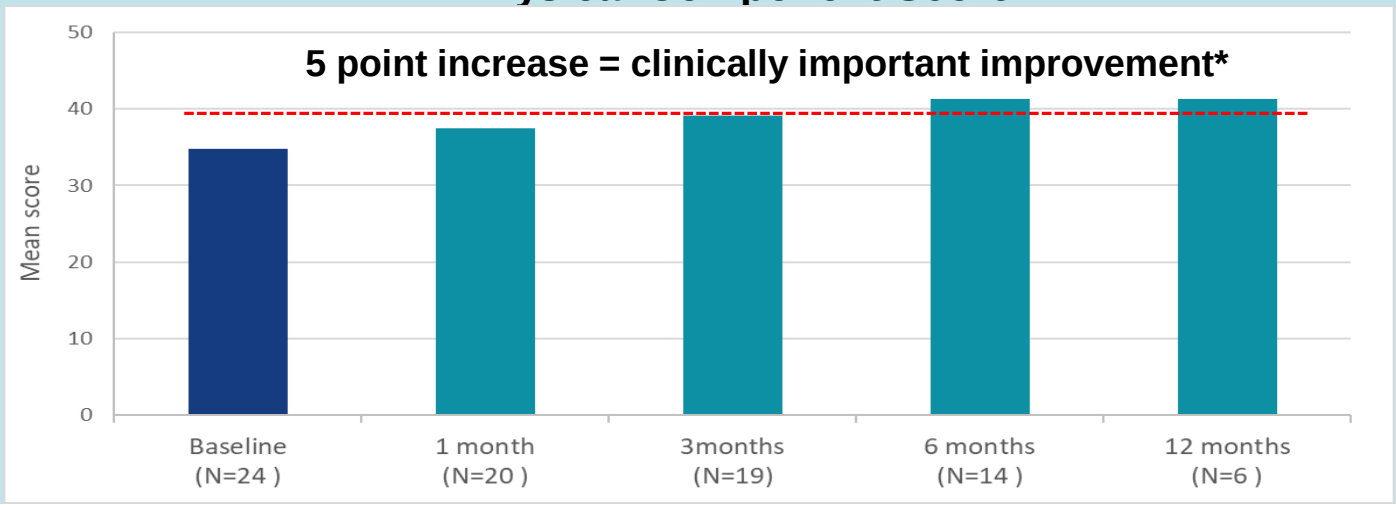
  - No unanticipated adverse device effects
  - Three patients experienced a composite primary safety event as adjudicated by CEC:
    - Hematuria after car accident – **alfa**pump explant — 1 in 1 patient
    - Wound dehiscence – **alfa**pump explant — 1 in 1 patient
    - Arterial injury during implantation – patient died — 1 in 1 patient

Roll-In Cohort: Clinically Important Improvement in Quality of Life Maintained up to 12 Months

SF-36

General health-survey questionnaire

Physical Component Score

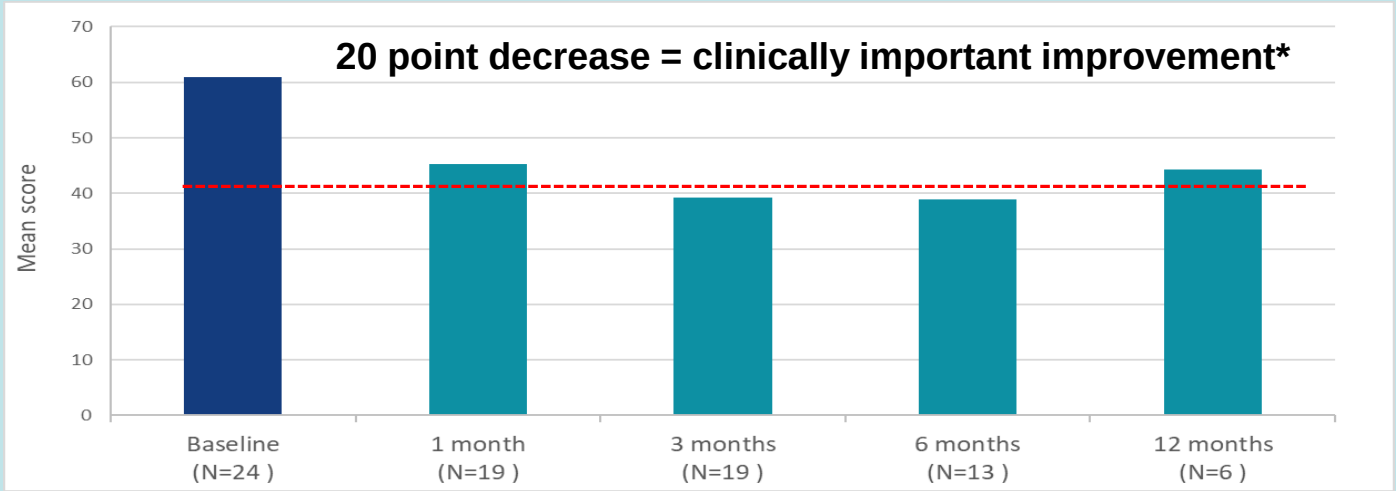


Higher is better

Ascites Q

Specific health-survey questionnaire for ascites

Total Score



Lower is better

** Clinically important improvement: exceeding the threshold for Minimal Clinically Important Difference*

alfapump® - the Challenge and Promise

- alfapump is well accepted
  - Patient reported outcomes are solid
  - Strong interest
- Safety
  - Less hepatic encephalopathy (HE)
  - Manageable infection rate
  - Decreased ascites burden
  - Less albumin need
- Can work in liver transplant environment
- Serves a population segment who needs therapy and may have difficult time accessing care

alfapump® - the Challenge and Promise (cont'd)

- TIPS may be viewed as a more permanent option
  - Outside of clinical trial, alfapump may deliver similar results without HE
- Albumin replacement protocols remain costly and potentially not fully beneficial
- Liver transplant (LT) is not an answer to all
  - May still bridge ascites control until LT available
- There may be a role for alfapump in palliative care where LT may not deliver

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Innovators in the treatment of diuretic-resistant fluid overload

liver disease – malignant ascites – heart failure

Two pillars of growth – € billion opportunities

alfapump®

Liver Disease (NASH)

Proven step change in liver refractory ascites and malignant ascites

Over 850 devices implanted

> €3 Bn / year market opportunity(1)

POSEIDON pivotal study ongoing

Self-commercialisation

alfapump DSR®

Heart Failure

Breakthrough approach to diuretic-resistant congestion

Proven ability to manage fluid balance, restore diuretic response & improve cardio-renal function

> €5 Bn / year market opportunity(2)

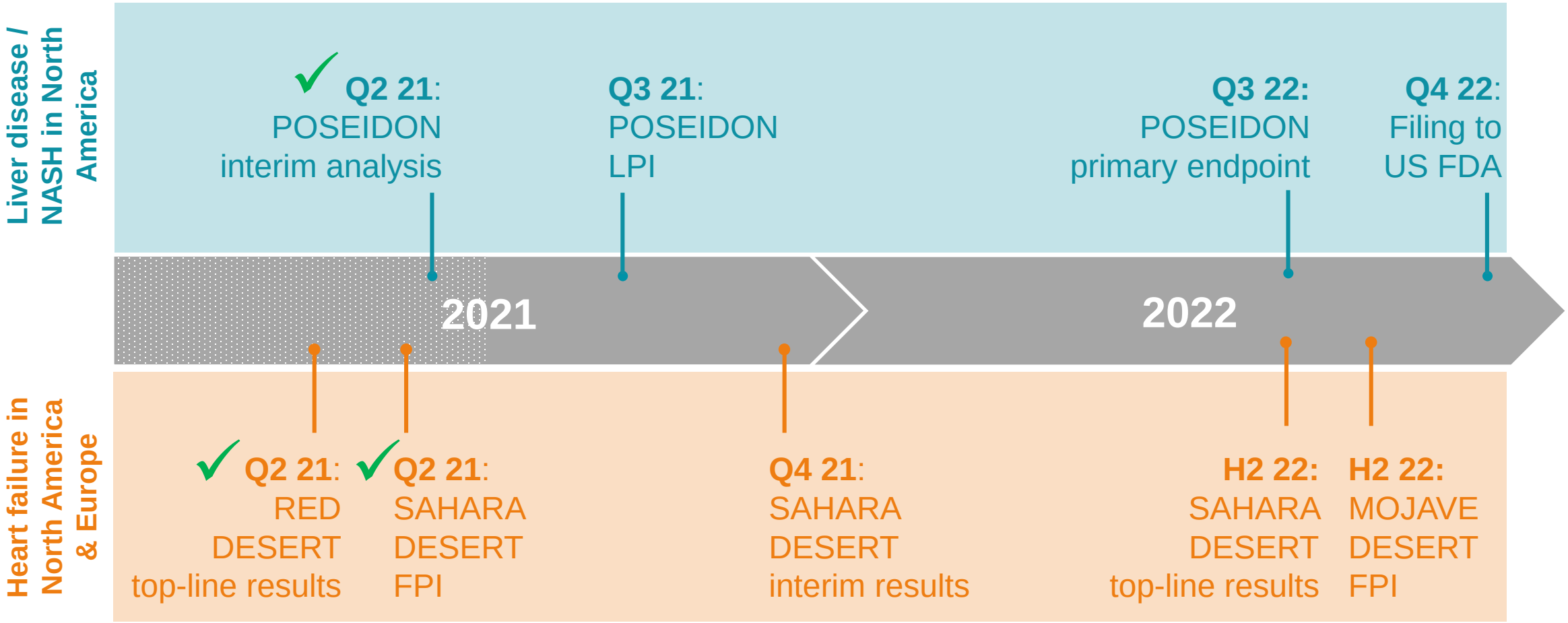
SAHARA DESERT study ongoing

Partnering after US efficacy study

Built upon proven European clinical & commercial experience

Source 1: Management estimate in US within 10-20 years, that is inclusive of estimated growth in prevalence of NASH for the US based on GlobalData Epidemiology Forecast to 2026
Source 2: Management estimate in US & EU by 2026 based on GlobalData Heart Failure Epidemiology Forecast to 2026; Costanzo et al. (2007). Kiglore et al (2017)

Expected core value drivers & outlook



Note: Presented timelines are subject to further developments related to the COVID-19 pandemic

FPI: *First Patient In;* ***LPI:*** *Last Patient In*

Q&A

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