Endotoxin and Intravenous Therapy
Clinical Update on Endotoxin and Intravenous Therapy

Clinical Problem
Gram negative bacteria produce endotoxin:
Endotoxin forms a major part of the outer layer of Gram-negative bacterial cells. It is shed in small amounts during the life of the cell and liberated in large quantities when cell death and lysis occurs. The presence of phosphate groups on the lipid part of the endotoxin structure gives a high negative charge to the fragments of endotoxin that are released.

Endotoxin has adverse clinical effects
As well as inducing antibody production, endotoxin has a range of adverse effects on the body. At low levels, fever and malaise are experienced, this can progress to changes in the coagulation system, hypotension, vascular changes and multiple organ dysfunction syndrome, with increasing endotoxin exposure.
Endotoxin can arise in the body from endogenous or exogenous sources. The gut has a large population of Gram-negative bacteria and translocation of endotoxin from here has been implicated in endotoxic shock and multiple organ failure. Septic foci, Gram-negative sepsicaemia and other sources such as contaminated infusions and dialysate have also been linked to endotoxic shock.

Even small amounts of endotoxin can have clinical effects
All intravenous preparations are tested for the presence of endotoxins and must comply with stringent regulations. The USP limit for IV drugs and solutions is based on a maximum dose of endotoxin of 5 EU/kg/day, this equates to no more than 0.35 EU/ml if a total infusion volume of 1 litre is given to a 70kg patient.

Many endotoxin - producing bacteria grow rapidly in infusion fluids
In IV therapy, the ability of Gram-negative bacteria to grow rapidly in simple IV fluids has been demonstrated and several authors have reported outbreaks of Gram-negative sepsicaemia in which contaminated infusates were implicated.

Endotoxin can pass through most IV filters
The potential risk of endotoxin release from accumulated bacterial contamination in infusion systems is recognised.
It has been demonstrated that a continuous infusion of endotoxin can originate solely from a population of Gram-negative bacteria present in an in-line filter set.

As a result of this observation it is recommended that conventional IV filters are changed daily.\textsuperscript{13}

**Endotoxin retention is possible with an appropriate filter membrane**

The endotoxin aggregate shed from the cell is a particle with a high negative charge. It is possible to retain these aggregates by the incorporation of a positive charge, at an appropriate density and configuration, in the filter membrane.

Several authors have examined the ability of various membrane materials to retain endotoxin.\textsuperscript{14-17}

**Testing filters for endotoxin retention should truly simulate the clinical situation**

Since endotoxin arises in infusions from a population of Gram-negative bacteria, this situation should be simulated when IV filters are being tested for clinical use. The use of purified endotoxin, such as laboratory Reference Standard Endotoxins, is not appropriate. These purified preparations are much more soluble and of a considerably smaller aggregate size than the natural endotoxin that is encountered in clinical practice; other compounds are often added to the extracted endotoxin that affect the behaviour of the endotoxin in solution and testing.

The challenge level used in endotoxin retention testing should also be clinically significant. Previous work\textsuperscript{13} has shown that 0.7 EU/ml can accumulate in three days in an infusion system contaminated with less than 100 viable bacteria.

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Endotoxin retention by IV filter membrane.
Summary

- Gram negative bacteria produce endotoxin.
- Endotoxin has adverse clinical effects.
- Even small amounts of endotoxin can have clinical effects.
- Many endotoxin producing bacteria grow rapidly in infusion fluids.
- Endotoxin can pass through most IV filters.
- Endotoxin retention is possible with an appropriate filter membrane.
- Testing filters for endotoxin retention should truly simulate the clinical situation.

References

1. Retoshel CT and Brade H; Scientific American August 1992; p26-33.
6. United States Pharmacopoea XI