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Temocillin protein binding is concentration-dependent and not restricted to albumin.

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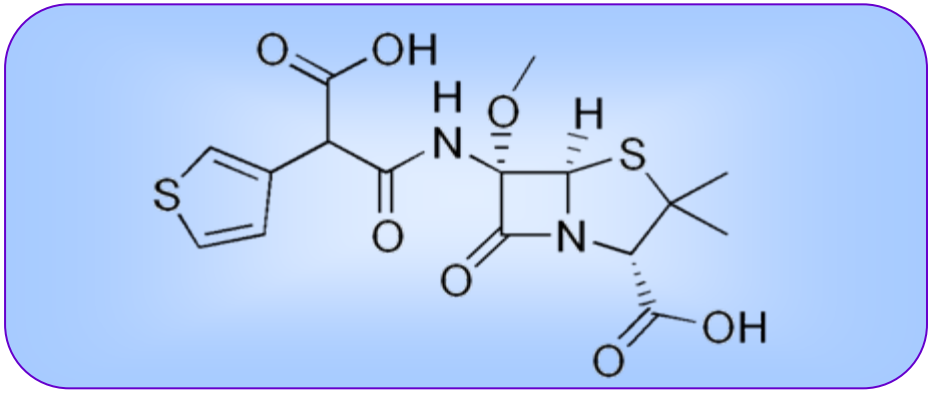
Temocillin



- 6-α-methoxy-ticarcillin
- Spectrum directed only against Gram negative bacteria with the exception of non-fermenters (*Pseudomonas aeruginosa*, *Acinetobacter* spp.)
- active against all producers of β-lactamase(s), including ESBL and AmpC
- Indications
  - urinary tract infections
  - Gram negative nosocomial infections (LRTI, IAI, bacteremia, …)

Background

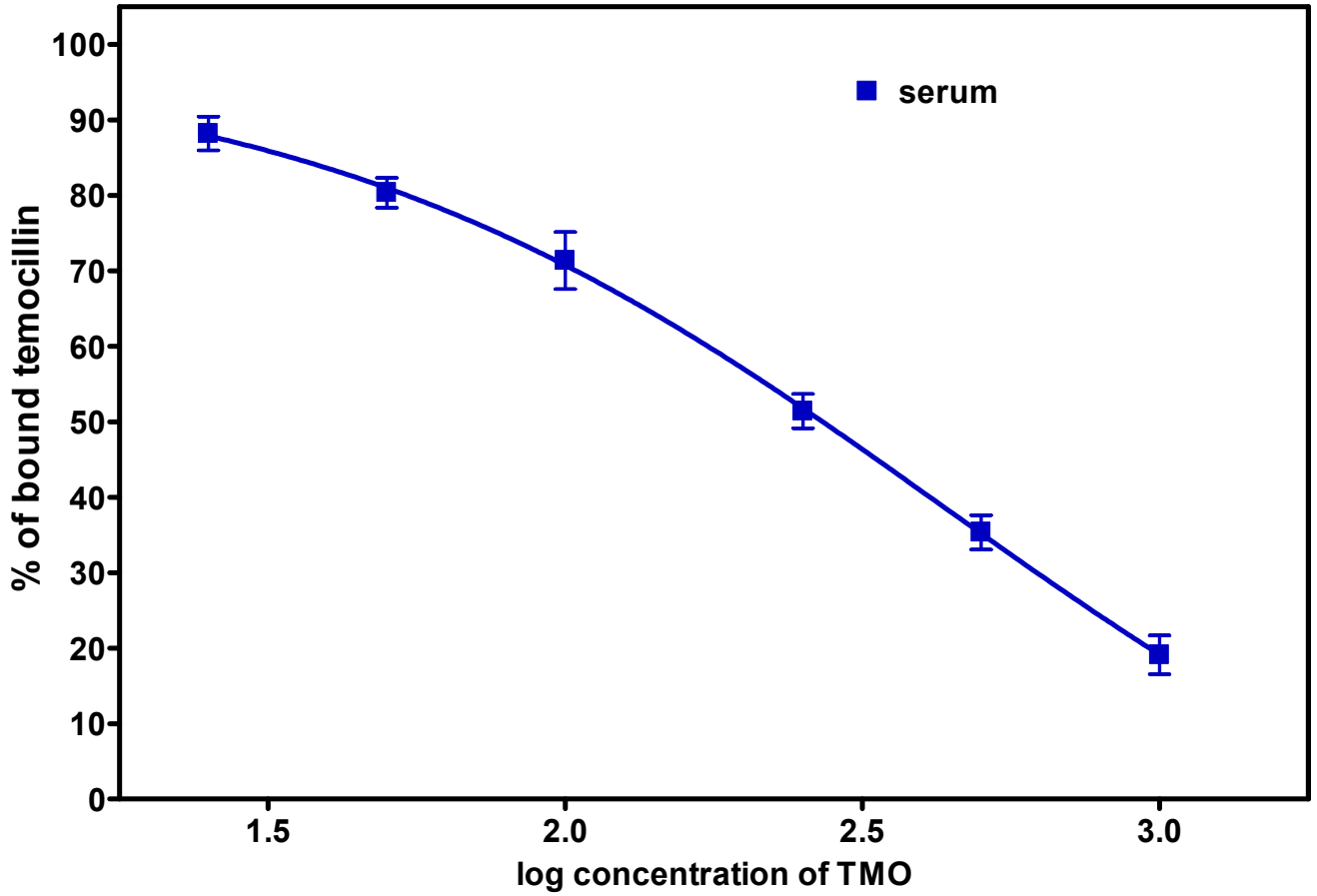
- **Temocillin is highly protein bound in healthy volunteers : 85%** (Overbosch, Drugs, 1985)
- **However TMO is less protein bound in critically ill patients** (De Jongh et al. JAC 2008)
  - **2g q12h : ~ 75%**
  - **4g / 24h in continuous infusion : ~ 70%**
- **This variability could have a major therapeutic impact as it is generally presumed that only the free fraction is active**

Aim of the study

- Determine the protein binding concentration profile of temocillin to human serum
- Compare the serum binding profile with the purified Human Serum Albumin binding profile

TMO binding to human serum

- TMO concentrations ranging from 25 up to 1000 mg/L
- Free concentration measured by HPLC after ultracentrifugation



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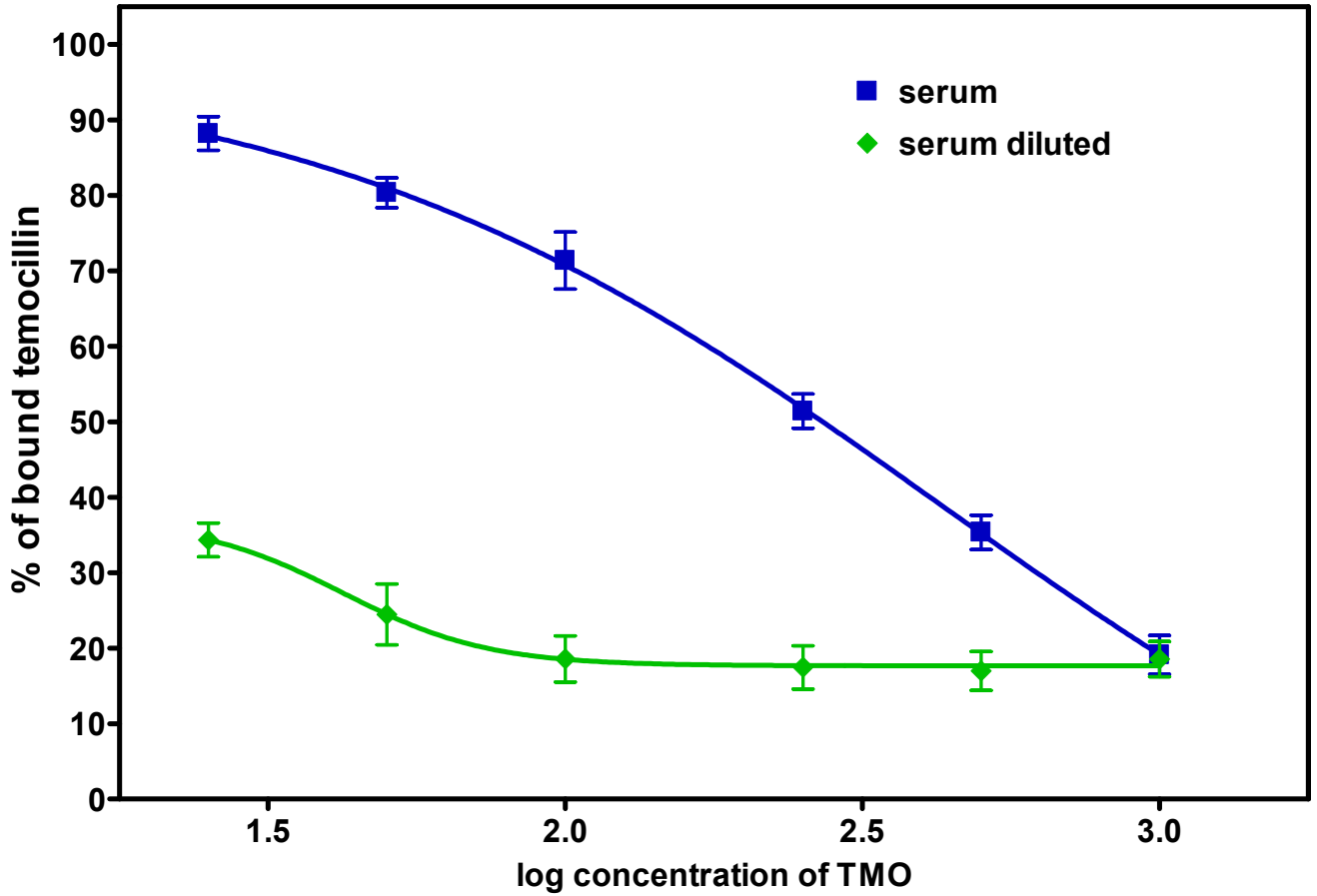
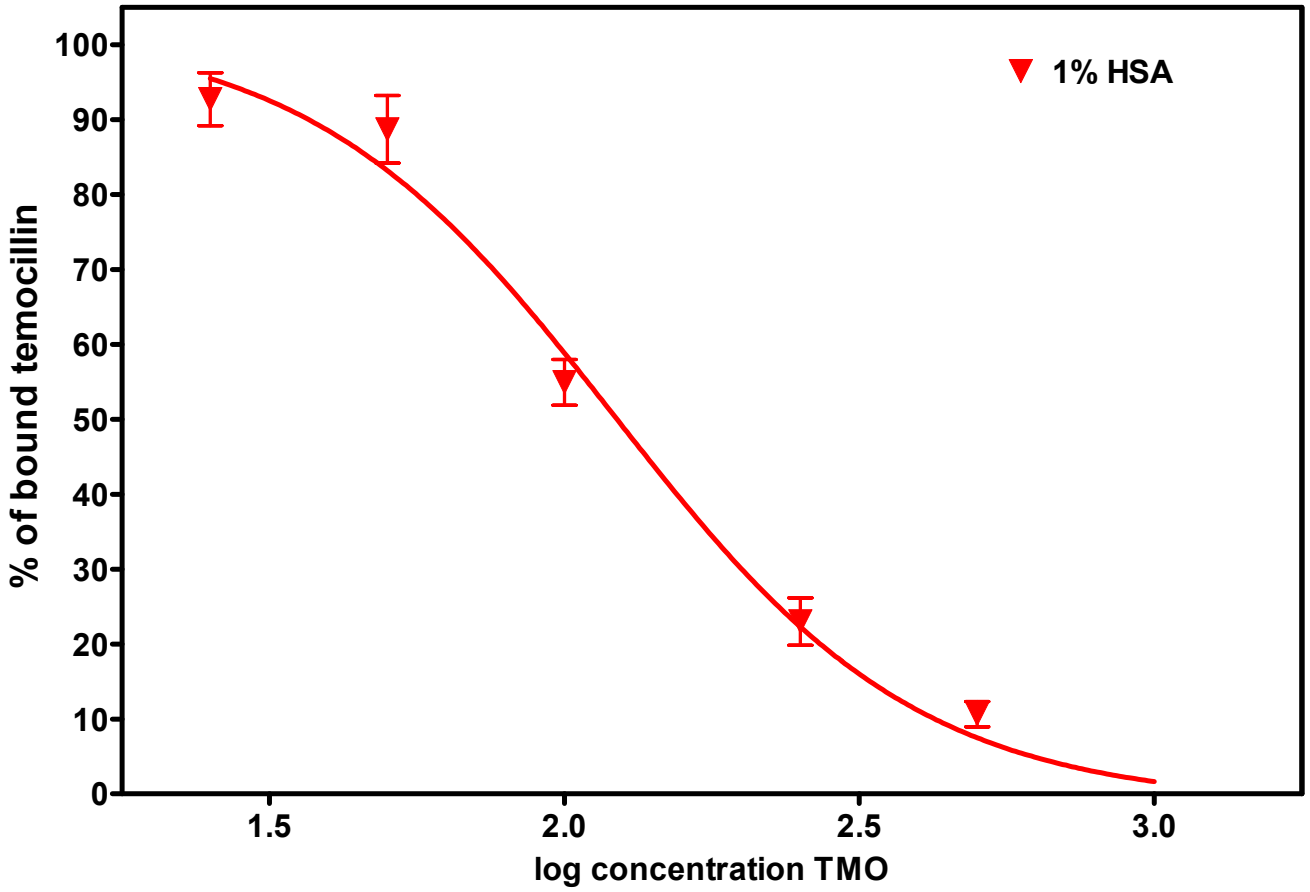


TMO binding to Human Serum Albumin

- TMO concentrations ranging from 25 up to 1000 mg/L
- HSA concentration in water ranging from 1 up to 5%
- Free concentration measured by HPLC after ultracentrifugation



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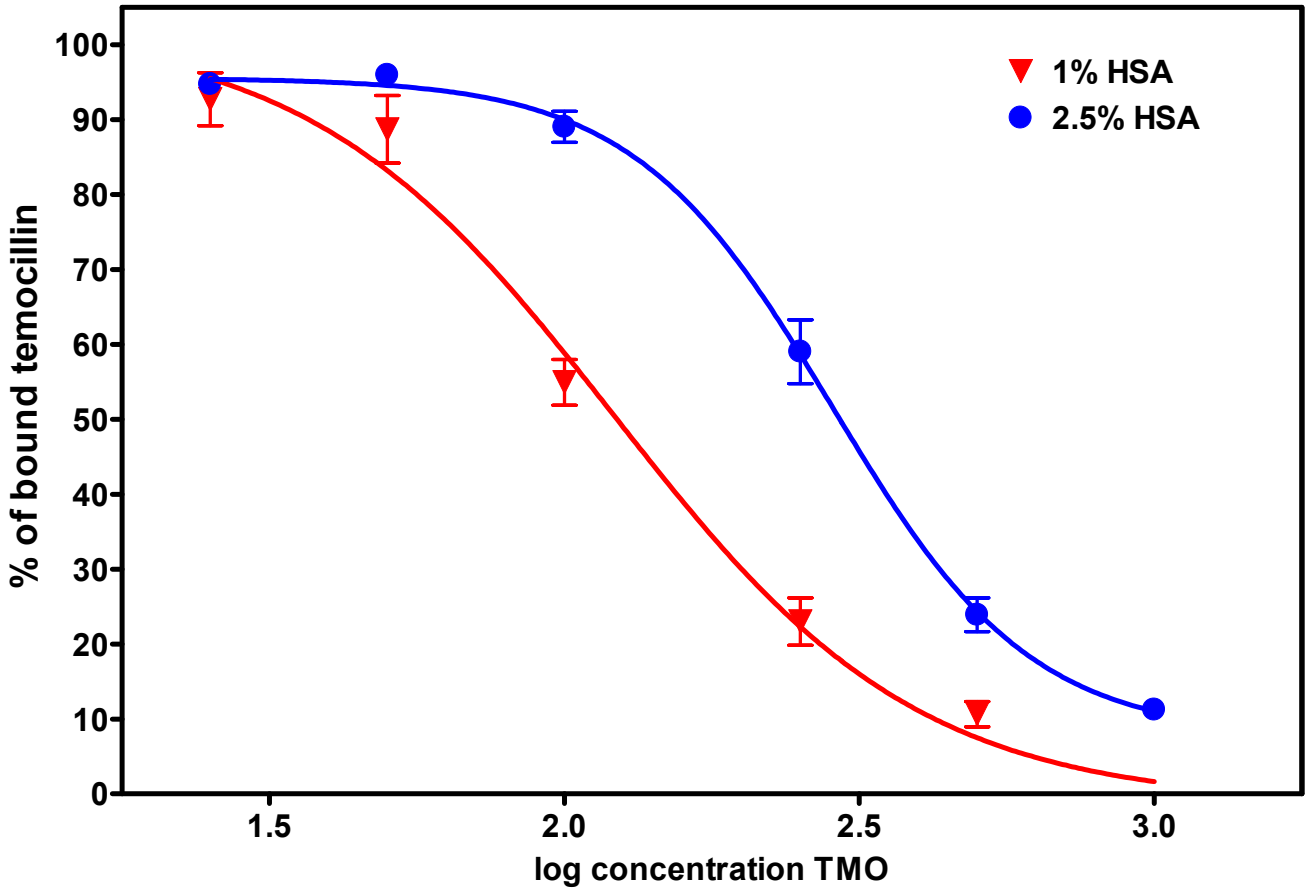

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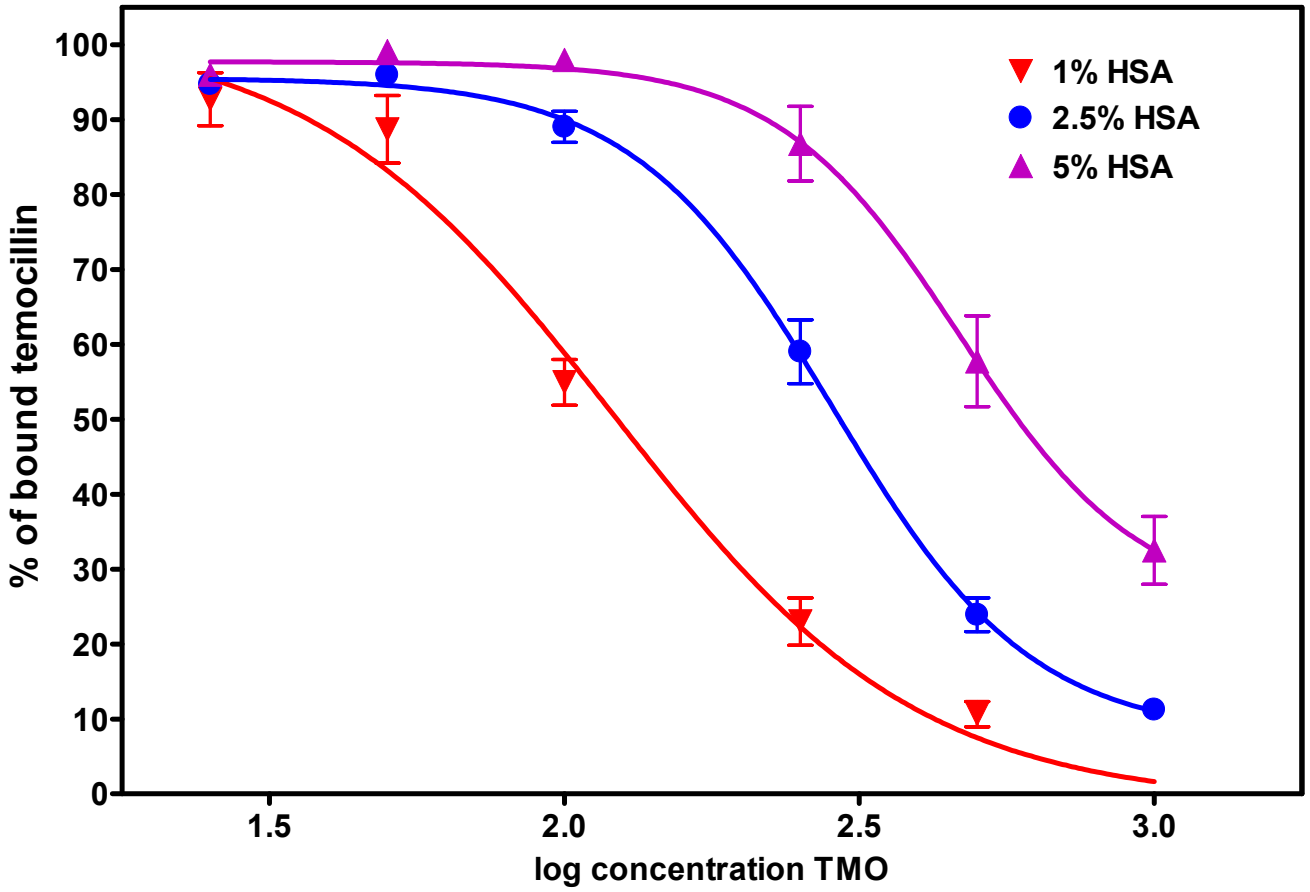

Discussion

Matrix	Max binding %	Min binding %	EC_{50} mg/L	slope
HSA 1%	96	3	121	- 2.14
HSA 2.5%	96	11	284	- 3.28
HSA 5%	96	38	514	- 4.35
serum	86	3	329	- 0.8

- For HSA, EC_{50} are proportional to the HSA concentration
- Min binding is increasing with the HSA concentration
- For serum, max binding corresponds to the binding in healthy volunteers
- The slope for serum is less steep than for HSA

Conclusions

- Temocillin protein binding is concentration-dependent
- Considering the normal concentration of of HSA in serum (~ 4%), the shape of the curves, and the maximum binding observed in serum, our data suggest that other factors are involved and perhaps that temocillin binds not exclusively to albumin
- These data might explain at least partially what has been observed in critically ill as these patient often present low serum protein levels