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Mathematical Modelling of the Concentration of Microorganisms in the Urinary Bladder under Simple Conditions

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Summary

Mathematical relationships for simple models of the filling and evacuation of the urinary bladder have been found and analyzed. These make the determination of the concentration of microbes in the urinary bladder at a given moment possible in relation to different parameters such as the rate of urine flow from the ureters, the microbe concentration in urine, the reproduction rate of microorganisms, the capacity of the urinary bladder and the size of the residue which remains in the bladder after miction.

Key words

Concentration of microorganisms in urine – Mathematical analysis – Mathematical modelling

Introduction

It has been known for a long time from medical practice that any congestion of urine when its flow is impaired or delayed may act as a factor which facilitates the development of infection of urinary pathways. It may be assumed that the cause of this phenomenon may be due to an increased concentration of microorganisms in the stagnating urine. The urinary bladder is the organ which is relatively frequently affected by infectious inflammations. We were therefore interested to know how the concentration of microbes in the urinary bladder changes in relation to some circumstances such as the rate and time of its filling, its capacity (volume) and the concentration of microbes in urine which enters the urinary bladder from the ureters.

Incomplete evacuation of the urinary bladder is frequently the cause of cystitis. This may be associated with the fact that in the urinary bladder where a certain residue remains after miction, the microbe concentration is higher than under normal conditions.

Our attention was focused on the principles and mathematical laws, which determine the urinary concentration of microorganisms under the given circumstances at a given time in the urinary bladder, rather than on the actual values.

Methods

We considered three simple model situations and attempted to find the mathematical relationships which govern the concentration of microorganisms in the urinary bladder during these situations.

Situation 1: The urinary bladder is completely evacuated after miction.

Situation 2: The urinary bladder is permanently filled and the urine only flows through the bladder (so-called "overflowing bladder", e.g. in nervous diseases or post-traumatic conditions).

Situation 3: The urinary bladder is incompletely evacuated after miction. The bladder evacuates after filling but a residual volume remains there.

The capacity of the urinary bladder (or the volume, when urination starts) is described as **V** [ml], its residual volume $\mathbf{V_0}$ (for situation 3), the rate of urine flow from the ureters **Q** [$ml.min^{-1}$], the concentration of microorganisms in the inflowing urine **c** [ml^{-1}] and the time taken by the microbes to reproduce to twice the original number $\mathbf{T_2}$ [min]. The time when the concentration of microorganisms assessed in the urinary bladder is described as **t** [min]. We also introduced the concept constant of reproduction of microorganisms **k** [min^{-1}] where the following relationships holds:

$$\mathbf{k} = \ln 2/\mathbf{T_2}$$

For the sake of simplification, we assumed that values **Q**, **c**, T_2 and **k** do not change with time and remain constant. The urinary bladder wall is impermeable for microbes which cannot penetrate into the bladder across its wall or escape from it by this route. We are aware that this does not correspond fully to the actual situation. This applies in particular to the assumed constant value of T_2 and **k**.

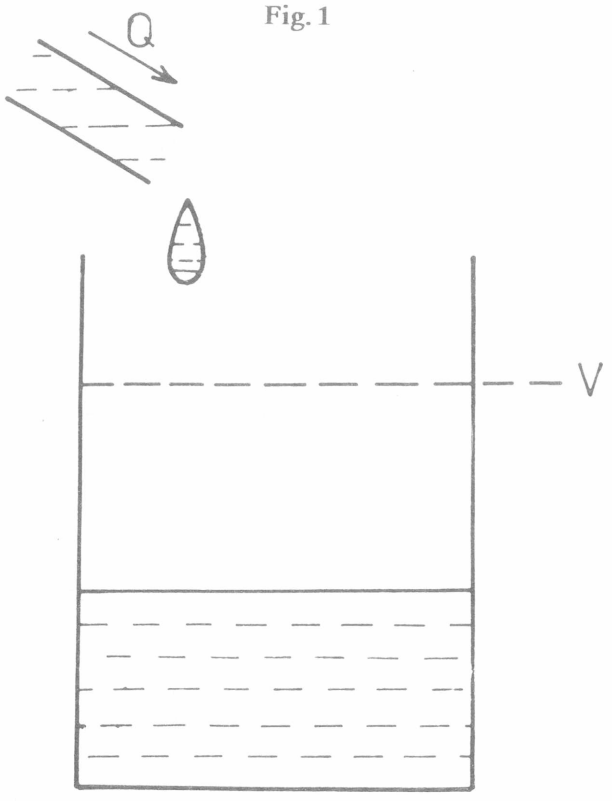
For the three model situations, mathematical relationships were elaborated which determine the relation between the microbe concentration in urine in the urinary bladder and factors **t**, **Q**, **c**, T_2, **k**, **V** and V_0. For illustration, the actual microbe concentrations in urinary bladder urine in relation to time we also ascertained for certain selected values of parameters **Q**, **c**, T_2, **k**, **V** and V_0.

Results

Situation 1 (Fig. 1)

At zero time (t_0) the urinary bladder is empty. The microorganisms which penetrate into the bladder reproduce at a rate which can be expressed by means of the reproduction constant **k**. Their amount in the urinary bladder is described as **M**.

Fig. 1



Evidence can be provided that in this case the rate of change of the amount of microorganisms in the urinary bladder $d\mathbf{M}/dt$ can be expressed by the differential equation:

$$d\mathbf{M}/dt = \mathbf{c}.\mathbf{Q} + \mathbf{k}.\mathbf{M} \qquad (1)$$

As at time $\mathbf{t} = 0$, $\mathbf{M} = 0$ (the urinary bladder is empty), equation (1) can be solved as follows (Rescigno and Serge 1966, Snell 1967):

$$d\mathbf{M}/dt = \mathbf{c}.\mathbf{Q}.e^{kt}$$

For the amount of microbes in the urinary bladder at time **t**, described as $\mathbf{M}_t$, thus holds:

$$\mathbf{M}_t = \int_0^t \mathbf{c}.\mathbf{Q}.e^{kt}$$

after adjustment: $$\mathbf{M}_t = \mathbf{c}.\mathbf{Q}\,(e^{kt} - 1)/\mathbf{k} \qquad (2)$$

The total amount of urine in the bladder at time **t** ($\mathbf{V}_t$) is the product of **Q** and **t** ($\mathbf{V}_t = \mathbf{Q}.\mathbf{t}$).

For the microbe concentration in time **t** ($\mathbf{c}_t$) the following relationship holds:

$$\mathbf{c}_t = \mathbf{M}_t/\mathbf{V}_t$$

after adjustment: $$\mathbf{c}_t = \mathbf{c}.(e^{kt} - 1)/\mathbf{k}.\mathbf{t} \qquad (3)$$

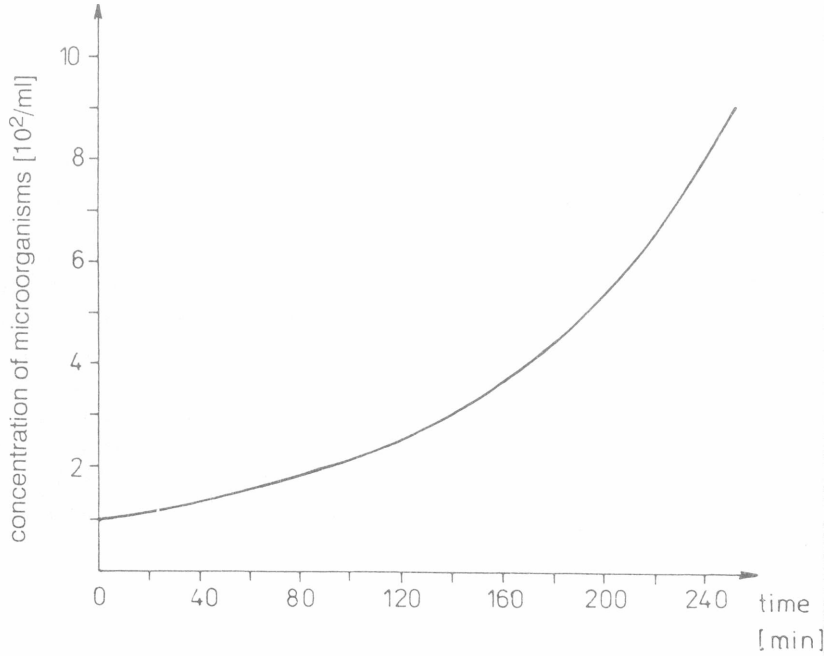
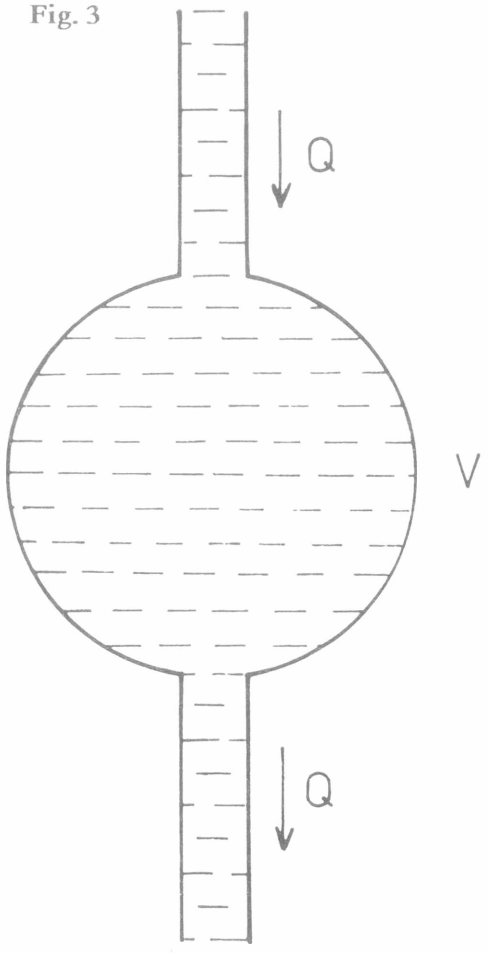


Fig. 2 *illustrates the concentration of microorganisms in the urinary bladder as a function of time for selected parameters* $\mathbf{Q} = 2\ ml.min^{-1}$, $\mathbf{c} = 100\ ml^{-1}$, $\mathbf{V} = 500$ ml, $T_2 = 50$ min ($\mathbf{k} = 0.0139\ min^{-1}$)

Fig. 3



Situation 2 (**Fig. 3**)

The urinary bladder is permanently filled to volume **V**, urine flows constantly into the bladder at the rate **Q** and at the same time escapes from the bladder at the rate **Q**.

The rate of change in the amount of microbes in the urinary bladder $d\mathbf{M}/dt$ is expressed by the differential equation:

$$d\mathbf{M}/dt = \mathbf{c}.\mathbf{Q} + \mathbf{k}.\mathbf{M} - \mathbf{c}_x.\mathbf{Q} \qquad (4)$$

where $\mathbf{c}_x$ is the microbe concentration in the urinary bladder.

After a certain time the microbe concentration in the urinary bladder $\mathbf{c}_x$ attains a steady value, described as $\mathbf{c}_u$. If $\mathbf{c}_u$ does not change in the course of time, the following relationship also holds:

$$d\mathbf{M}/dt = \mathbf{0}$$

The differential equation (4) can then be solved as follows (Rescigno and Serge 1966, Snell 1967):

$$(\mathbf{k}.\mathbf{c}_u.\mathbf{V}) - \mathbf{Q}.(\mathbf{c}_u - \mathbf{c}) = \mathbf{0}$$

and after adjustment:

$$\mathbf{c}_u = \mathbf{c}.\mathbf{Q}/(\mathbf{Q} - \mathbf{k}.\mathbf{V}) \qquad (5)$$

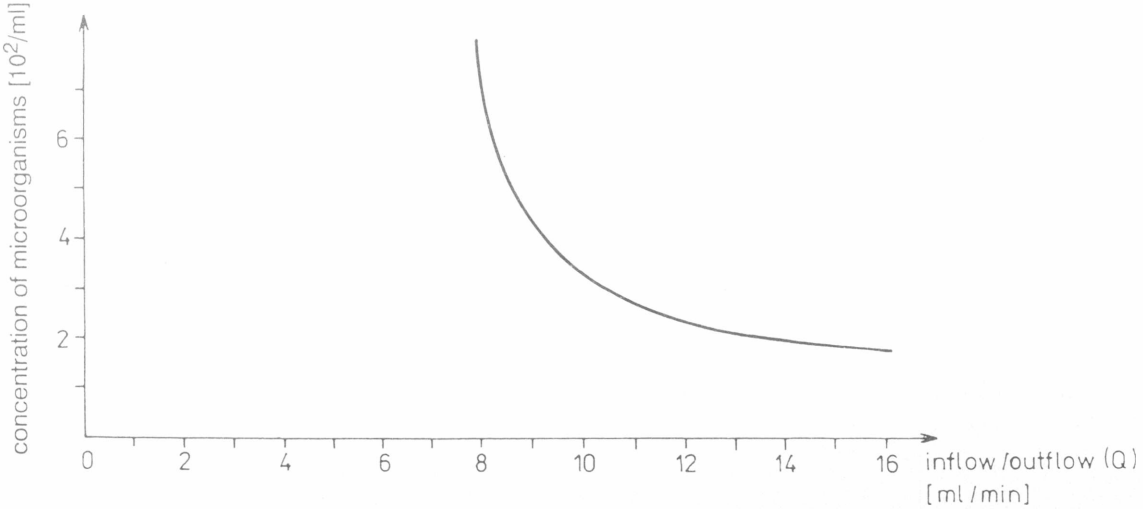
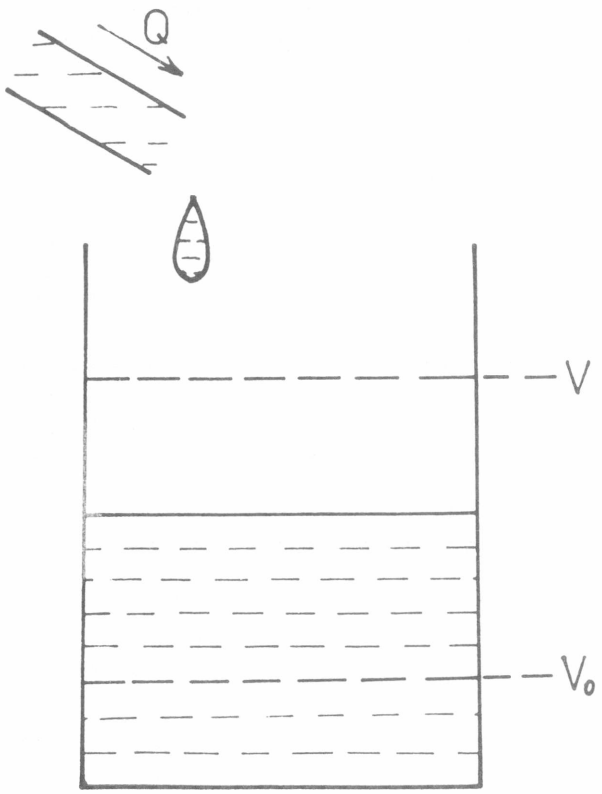


Fig. 4 *illustrates the relationship of the microbe concentration in the urinary bladder in the steady state (c_u) on the inflow rate (i.e. also the outflow rate) into the urinary bladder (and also out of it) for selected parameters* $\mathbf{c}$ = 100 ml^{-1}, $\mathbf{V}$ = 500 ml, $\mathbf{T}_2$ = 50 min ($\mathbf{k}$ = 0.0139)

Fig. 5



Situation 3 (**Fig. 5**)

The amount of microbes present in the urinary bladder at a certain moment is described as **M**. The rate of change of this amount in time, **dM/dt**, can be expressed by the following differential equation:

$$dM/dt = c.Q + k.M \qquad (6)$$

A certain residue remains after miction (i.e. at time $t=0$) in the urinary bladder with a volume V_0, where the concentration of microorganisms is c_0. Their amount M_0 in time $t = 0$ can be expressed by the relationship:

$$M_0 = c_0.V_0$$

The amount of microorganisms in the urinary bladder at time **t** (M_t) is assessed by solving the differential equation (6) (Rescigno and Serge 1966, Snell 1967):

$$M_t = (V_0.c_0.e^{kt}) + c.Q.(e^{kt} - 1)/k \qquad (7)$$

For the concentration of microbes in the bladder at time **t** (c_t) holds:

$c_t = M_t/(V_0 + Q.t)$ after adjustment:

$$c_t = [k.V_0.c_0.e^{kt} + c.Q.(e^{kt} - 1)]/k.(V_0 + Q.t) \qquad (8)$$

If the selected model situation is maintained for a long period of time, i.e. after filling of the urinary bladder to volume **V**, it is always evacuated to volume V_0 and parameters **Q**, **c** and **k** will not change, after many cycles of filling and evacuation of the bladder it will attain a steady state at a concentration c_0 which can be calculated from the relationship:

$$c_o = [k.V_0.c_0.e^{kt} + c.Q.(e^{kt} - 1)]/k.(V_0 + Q.t)$$

where we must substitute for **t** the right part of the relationship $t = (V - V_0)/Q$ After adjustment we obtain equation (9)

$$c_0 = c.Q.(e^{k.(V - V_0)/Q} - 1)/k.(V - V_0.e^{k.(V - V_0)/Q})$$

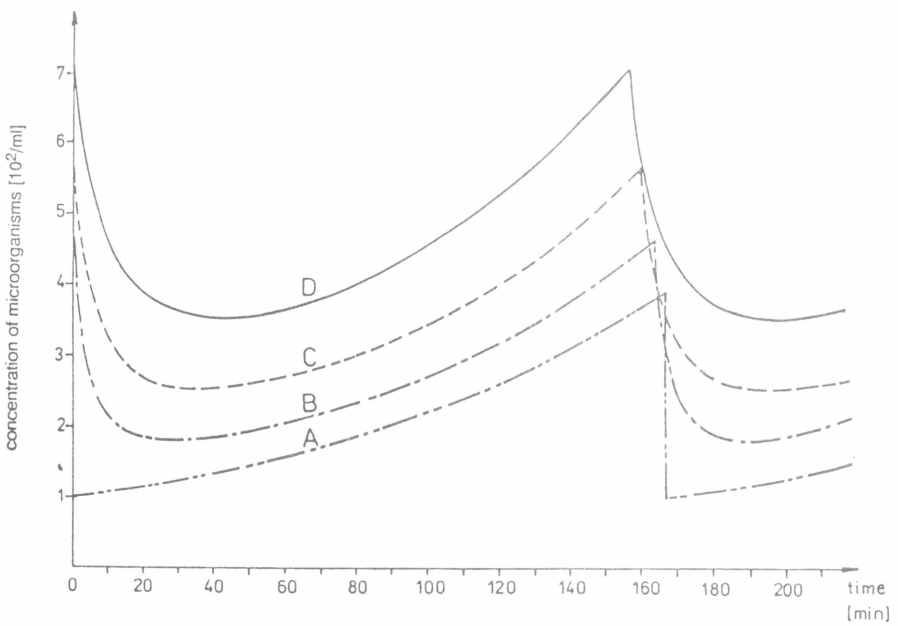
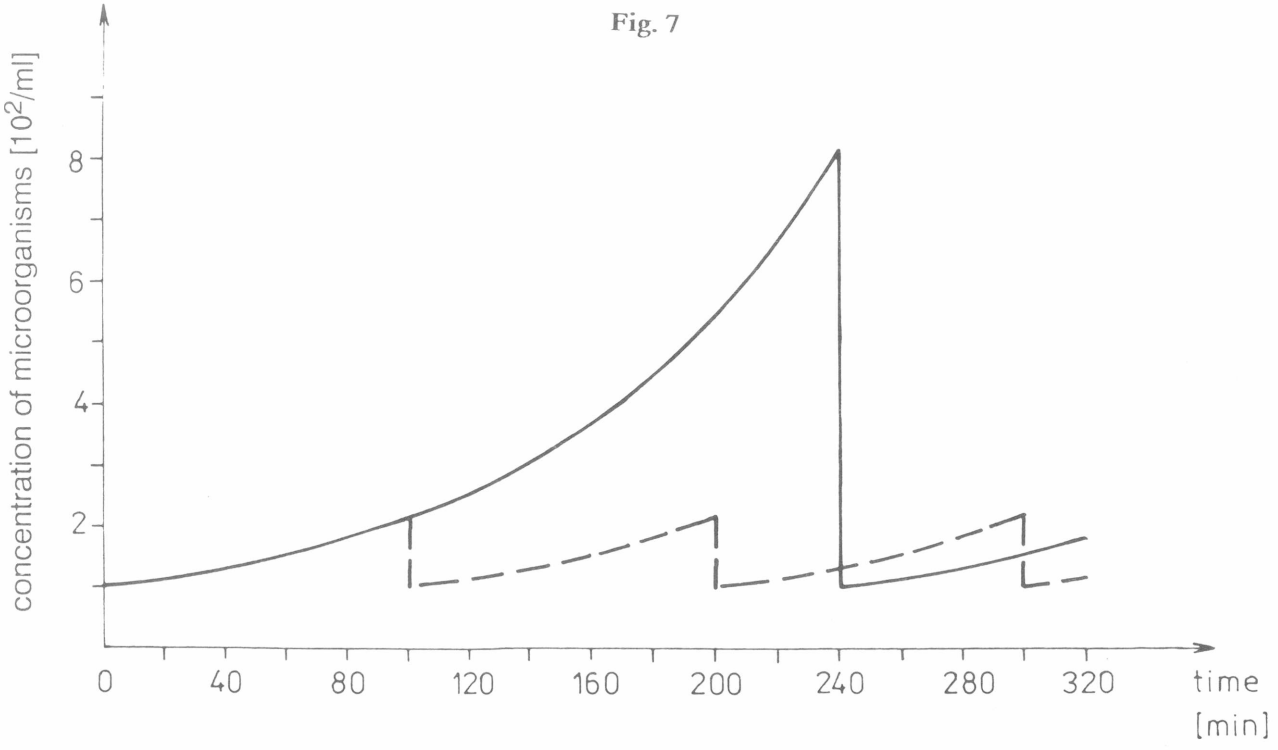


Fig. 6 *illustrates the relationship of the microbe concentration in time (in a steady state after many cycles of filling and emptying of the bladder) for the selected parameters:* **Q** = 3 ml.min^{-1}, **c** = 100 min^{-1}, T_2 = 50 min (**k** = 0.0139 min^{-1}), **V** = 500 ml where: A) V_0 = 0 ml, B) V_0 = 10 ml, C) V_0 = 20 ml, D) V_0 = 30 ml

Discussion

The model situations that were selected for assessment of the mathematical relationships which determine the microbe concentration in the urinary bladder are a certain simplification as compared with the actual situation. Thus in practice it cannot be assumed that the inflow of urine into the bladder takes place at a constant rate **Q**. The inflow rate of urine may change in the course of time with regard to various circumstances, e.g. the regime of fluid intake, fluid losses due to perspiration etc. Similarly, the microbe concentration in the inflowing urine need not be constant in the course of time. If it were possible to define mathematically the relationship of the inflow level and the microbe concentration in the inflowing urine, more complicated models of filling of the urinary bladder could be introduced than those given above. In practice, this would, however, be difficult and the actual information obtained from such models for real clinical situations would not obviously be substantial. Similarly, we can discuss whether it is correct that the rate of reproduction of microorganisms in the urinary bladder is expressed by a single invariable figure, i.e. the reproduction constant **k**. The situation may arise in practice that the urine contains simultaneously several microbe populations which reproduce at different rates. In that case the above derived relationships would hold for each population separately. However, the question whether the constant **k** can change in relation to the microbe concentration in urine is even more important. It is probable that with the rising microbe concentration their replication rate declines (starting at a certain concentration). The ensuing consequences for the validity of some relationships are discussed below.

Fig. 7



It ensues from relationship (3) that in *situation 1* during frequent urination the microbe concentration in the urinary bladder cannot reach as high values as in less frequent miction (**Fig. 7**). It is also apparent from equation (3) that, under these conditions, the microbe concentration in the urinary bladder does not depend on rate **Q** at which urine flows into the bladder. However, since it takes some time to fill the bladder, if the inflow rate of urine is low, the microbe concentration in the urinary bladder attains higher values just before miction.

It may even be considered that if the inflow rate of urine into the bladder is greater, the microbe concentration **c** may be lower. If we admit that during an n-fold increase of the inflow rate of urine the microbe concentration in the inflowing urine will be reduced n times, we may derive the following conclusion from equation (3):

If we describe the concentration of microorganisms in the urinary bladder just before its evacuation (after complete filling) as c_1, if the urine inflow from the ureters is at a rate **Q**, and c_2, if the inflow rate is n x **Q**, then the following relationship holds:

$$c_1/c_2 = (e^{k.V/Q} - 1)/(e^{k.V/n.Q} - 1) \qquad (10)$$

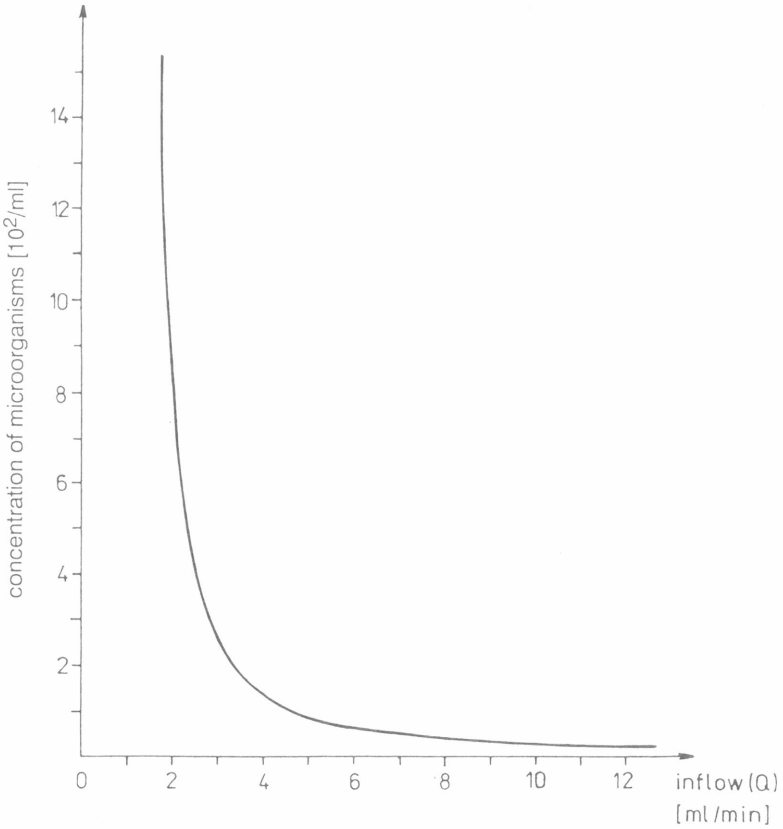


Fig. 8 *illustrates the concentration of microorganisms in the urinary bladder at the moment closely preceding its evacuation (after complete filling) in relation to the inflow value Q (assuming that the relationship (10) holds) for selected parameters:* $\mathbf{c} = 100\ ml^{-1}$ (at $\mathbf{Q} = 2\ ml.min^{-1}$), $\mathbf{T_2} = 50$ min ($\mathbf{k} = 0.0139\ min^{-1}$), $\mathbf{V} = 500$ ml

Increased fluid intake associated with more rapid urine formation leads to more rapid filling and thus also to more frequent evacuation of the urinary bladder. This is (obviously with a somewhat lower microbe concentration in the inflowing urine) manifested by a reduction of the attained microbe concentration in the urinary bladder and may play a favourable role in the treatment of cystitis.

Polakisuria which develops in infectious cystitis must have a positive biological impact in the sense that it reduces somewhat the maximal attained microbe concentration in the urinary bladder. Even in a healthy individual it is favourable if he urinates more frequently than necessary with regard to the capacity of his urinary bladder. The more frequent is the miction, the lower is the microbe concentration in the urinary bladder. Clinical experience is thus fully consistent with the conclusion derived from the mathematical relationships.

In *situation 2* the microbe concentration in the urinary bladder $\mathbf{c_u}$ attains a value determined by equation (5). Its value according to this equation is positive only when the following equation holds:

$$\mathbf{Q - k.V > 0} \text{ or } \mathbf{Q > k.V} \qquad (11)$$

If the values of parameters **Q**, **k** and **V** were mutually related then the following would hold:

$$\mathbf{Q - k.V \leq 0} \text{ or } \mathbf{Q \leq k.V} \qquad (12)$$

according to equation (5) the $\mathbf{c_u}$ value would be negative if we would shift beyond the defining range of equation (5) when calculating $\mathbf{c_u}$. In practice, this would be consistent with a situation when a steady state cannot be attained in the urinary bladder at given values of parameters **Q**, **k** and **V**, i.e. when the microbe concentration in the bladder steadily increases with time. Under actual conditions, this would lead to a certain delay of microbe replication, i.e. a decline of the reproduction constant **k** so that the initial assumption that this value remains constant in time would not hold. The decline of the value would have to be so marked that the relationship (12) would no longer be true and relationship (11) would hold instead. Thus a steady state could develop and the microbe concentration would remain at a constant level.

It is obvious from Fig. 6 that in *situation 3* the microbe concentration in the urinary bladder at a certain period of time first declines, which is apparently due to "dilution" of the urine, which remains in the bladder as a residue, by the urine which enters the bladder. After some time, however, the rate of microbe replication is greater than the rate of urine dilution and the microbe concentration in the urinary bladder begins to increase. If the whole cycle of filling and subsequent incomplete emptying of the bladder occurs repeatedly several times while the parameters are unchanged, at first the concentration of microorganisms in time is different in every cycle, since there are different amounts of

microorganisms in the residue at the onset of every cycle. After many cycles, however, a steady state is established and the microbe concentration in the urinary bladder in relation to time takes the same course in all cycles. Its magnitude $\mathbf{c}_0$ just before miction (and in the residues left in urinary bladder) can be determined from equation (9).

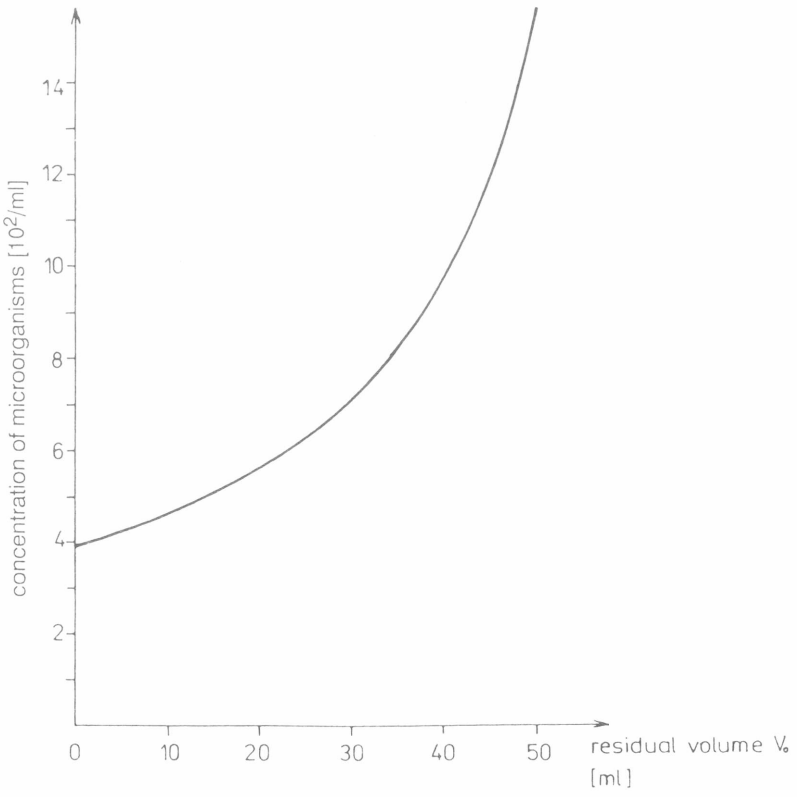


Fig. 9 *indicates which microbe concentration in the urinary bladder would be in a steady state just before miction (c_0) in relation to the size of the residue V_0 for the selected parameters:* $\mathbf{Q} = 3$ ml.min^{-1}, $\mathbf{c} = 100$ ml^{-1}, $\mathbf{T}_2 = 50$ min ($\mathbf{k} = 0.0139$ min^{-1}), $\mathbf{V} = 500$ ml

It can be deduced from Fig. 9 that under the given conditions (for a residual volume $\mathbf{V}_0$ smaller than 65 ml) the microbe concentration which is attained in the urinary bladder rises markedly with an increasing residual volume $\mathbf{V}_0$. This fact is also apparent from Fig. 6. It is consistent with the clinical experience that the greater is the residue which remains in the bladder after miction, the more likely is cystitis or uroinfection development.

It is remarkable that for higher $\mathbf{V}_0$ values (in the given case more than 70 ml) the magnitude of $\mathbf{c}_0$ calculated from equation (9) would have negative values. Such a situation obviously cannot arise in practice which means that one of the initial prerequisites of the calculations for the given conditions was not realistic. Thus the situation must be analyzed further.

It is obvious that the microbe concentration $\mathbf{c}_0$ for a non-zero $\mathbf{V}_0$ must be greater than the microbe concentration $\mathbf{c}$ and must have a positive value. However, value $\mathbf{c}_0$ calculated according to equation (9) is positive only in case that values the following holds:

$$\mathbf{Q}/\mathbf{k} > (\mathbf{V} - \mathbf{V}_0)/\ln(\mathbf{V}/\mathbf{V}_0) \qquad (13)$$

after adjustment:

$$\mathbf{Q}.\ln \mathbf{V} - \mathbf{k}.\mathbf{V} > \mathbf{Q}.\ln \mathbf{V}_0 - \mathbf{k}.\mathbf{V}_0 \qquad (14)$$

For some values of parameters $\mathbf{Q}$, $\mathbf{k}$, $\mathbf{V}$ and $\mathbf{V}_0$, however, the magnitude of $\mathbf{c}_0$ calculated according to equation (9) has a negative value or we may be beyond the definition range of relation (9). It can be demonstrated that for positive values of parameters $\mathbf{Q}$, $\mathbf{k}$, $\mathbf{V}$ and $\mathbf{V}_0$ this is always the case, if the following holds:

$$\mathbf{Q}/\mathbf{k} \leq (\mathbf{V} - \mathbf{V}_0)/\ln(\mathbf{V}/\mathbf{V}_0) \qquad (15)$$

after adjustment:

$$\mathbf{Q}.\ln \mathbf{V} - \mathbf{k}.\mathbf{V} \leq \mathbf{Q}.\ln \mathbf{V}_0 - \mathbf{k}.\mathbf{V}_0 \qquad (16)$$

The practical explanation of this finding is that under the given conditions (if the relationship (15) and (16) holds) for parameters $\mathbf{Q}$, $\mathbf{k}$, $\mathbf{V}$ and $\mathbf{V}_0$ a steady state cannot develop even after an infinite number of cycles. This means that if the conditions given by equations (15) and (16) are met, the microbe concentration in the urinary bladder would theoretically rise steadily with the increasing number of cycles. This cannot be the case in clinical practice. The explanation for it is based upon the fact that with the increasing microbe concentration in the urine one of the parameters, which was originally considered to be constant, must change. This applies, no doubt, to the reproduction constant $\mathbf{k}$. The latter diminishes if the microbe concentration in the urine is high, i.e. that the microorganisms replicate more slowly at higher concentrations. Reduction of constant $\mathbf{k}$ leads

to an increase in the left side of equations (15) and (16) and the inequality changes to such an extent that equations (13) and (14) begin to hold and a steady state develops where the urinary microbe concentration does not rise any further.

From that what has been mentioned it is obvious that some of the presented relationships ((3), (5), (8) or (9)) cannot be applied in situations when the microbe concentrations in the urinary bladder reach high values. This obviously applies also to the graphs calculated from these relationships, using actual values of different parameters. Therefore the question arises whether it would not be expedient to create other models which would express the dependence of the reproduction rate on the urinary microbe concentration. If e.g. for value **k** the following simple relationship would hold:

$$\mathbf{k} = \mathbf{k}_0.(1 - \mathbf{c}_t/\mathbf{c}_{max})$$

then for *situations 1* and *3* following initial relationship could be used instead of relationships (1) and (6):

$$d\mathbf{M}/dt = \mathbf{c}.\mathbf{Q} + \mathbf{k}_0.(1 - \mathbf{c}_t/\mathbf{c}_{max}).\mathbf{M} \qquad (17)$$

and for *situation 2* the following relationship could be used instead of relationship (4):

$$d\mathbf{M}/dt = \mathbf{c}.\mathbf{Q} + \mathbf{k}_0.(1 - \mathbf{c}_t/\mathbf{c}_{max}).\mathbf{M} - \mathbf{c}_x.\mathbf{Q} \qquad (18)$$

where $\mathbf{k}_0$ is the magnitude of **k** at a microbe concentration close to 0, $\mathbf{c}_{max}$ is the maximal concentration which can be reached in urine by replication of microorganisms. The magnitude of $\mathbf{c}_{max}$ depends on a number of circumstances and for many pathogenic microbes it is obviously greater than 10^6/ml. It can be demonstrated that if $\mathbf{c}_{max}$ is substantially greater than $\mathbf{c}_t$, equations (1) and (17) or (2) and (18) do not differ significantly. The disadvantage of relationships (17) and (18) is that they are so-called non-linear models and that they cannot be solved by an analytical approach, i.e. it is impossible to find for them general functions analogous to relationships (3), (5), (8) and (9) which would express the dependence of the urinary microbe concentration on individual parameters. In that case only a numerical solution for the actual values of parameters could be used. It is important to mention that even equations (17) and (18) or similar ones could not completely describe the actual situation and that the information which they provide is not significantly superior to information provided by the above assumed linear models. Therefore we did not deal in the submitted paper with their numerical solution.

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Reprint Requests

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