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Viability of Microorganisms in Selected Cytostatic Drug Solutions

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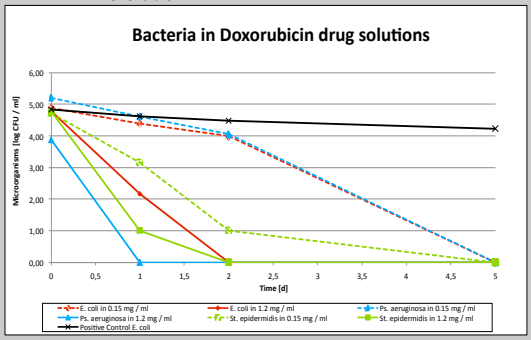
INTRODUCTION

For the production of cytostatic drug preparations at our institution, multidose vials, suited for multiple withdrawals, are used. Some studies revealed high bacterial contamination rates in multidose vials.[1] Therefore, strict aseptic conditions are mandatory and microbial aspects must be considered. The aim of this study was the examination of the viability of four facultative pathogenic microorganisms, each in four different, frequently used cytostatic drug solutions.

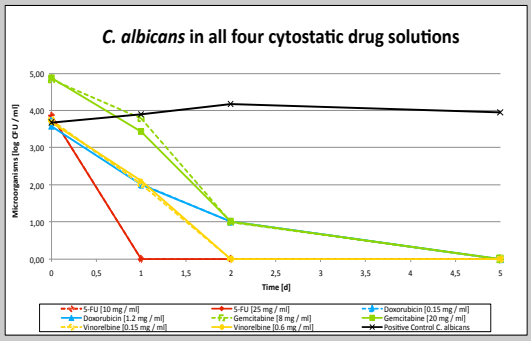
METHODS

Each drug was diluted with NaCl 0.9%, obtaining the following final concentrations: **5-Fluorouracil** (5-FU) 10 and 25 mg/ml, **Doxorubicin** 0.15 and 1.2 mg/ml, **Gemcitabine** 8 and 20 mg/ml, **Vinorelbine** 0.15 and 0.6 mg/ml. Of each drug and concentration, three samples were individually inoculated with four selected microorganisms (*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Candida albicans*), resulting in an inoculum concentration of 10^5 microorganisms per ml. As positive control, pure NaCl 0.9% solution was inoculated. The inoculated drug and control solutions were incubated at 30-35°C in Eppendorf 96/1000 µl deepwell plates. Samples were withdrawn after 0, 24, 48 and 120 hours, diluted 1:100, transferred to sheep blood agar culture medium and incubated at 30-35°C. Colony forming units were counted visually after 48 hours.

1 **Distinct concentration dependent bacterial viability in all four drug solutions – especially pronounced in Doxorubicin**



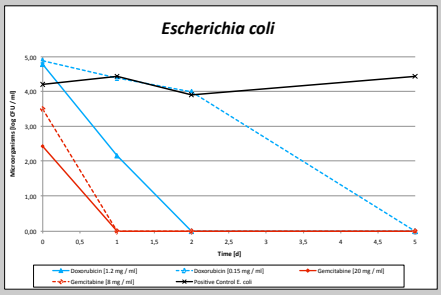
2 **No concentration dependent fungal viability in all four drug solutions**



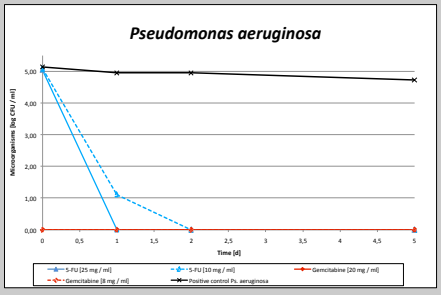
RESULTS

In total, 576 samples were taken. 5 days after inoculation, no growth was detected in all four cytostatic drug solutions, in contrast to the control solutions, in which the viable count remained stable over the 5 days study period. Bacteria and *C. albicans* showed distinctly different viability progressions in the cytostatic drug solutions (figures 1 and 2). Out of the four drugs studied, Gemcitabine was found to possess the strongest antibacterial activity (figures 3 and 4), whereas 5-Fluorouracil demonstrated the strongest antifungal activity (figure 2).

3 **Faster decrease of viability in Gemcitabine drug solutions compared to Doxorubicin**



4 **Instant decrease of viability in Gemcitabine drug solutions in contrast to 5-FU**



DISCUSSION - CONCLUSION

Differences in the progressions of viability of bacteria and fungi can be explained by their differing morphology.[2] The finding of antifungal activity of 5-FU is strengthened by the fact that 5-FU is also therapeutically used as a fungistat (as the prodrug 5-Fluorocytosine). Even though the four cytostatic drugs were found to possess antimicrobial activity, most microorganisms remained viable in the drug solutions for at least 24 hours. As most therapeutic drug solutions are intended to be used within the day of production, it is crucial that aseptic manufacturing is guaranteed.

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[1] Mattner F, Gastmeier P. Bacterial contamination of multiple-dose vials: A prevalence study. *AmJInfectContr* 2004; 32; 1. [2] Schlegel HG, Fuchs G. Allgemeine Mikrobiologie. 8th edition, *Georg Thieme Verlag GmbH*, Stuttgart DE, 2006.