

1 **Efficacy of pre-operative cephalosporin prophylaxis in controlling**
2 **pathogenic oral bacterial growth in comatose patients**

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22 Saliva contains many bacteria, and bad oral hygiene and periodontal diseases lead to
23 the proliferation of pathogenic bacteria that can cause aspiration pneumonia (Finegold, 1991,
24 Scannapieco, 1999 and The Japanese Respiratory Society, 2004). The etiologic role of
25 pathogenic flora in aspiration pneumonia is of special concern for neurosurgical patients
26 because the likelihood of long-term post-operative endotracheal intubation and
27 immobilization are additional risk factors for infectious complications involving the lungs
28 (Erman *et al.*, 2005 and Korinek *et al.*, 2005).

29 Administration of cephalosporins to patients as prophylaxis for high-risk surgical
30 procedures at the time of induction of general anaesthesia is routinely done in many institutes.
31 In this study the efficacy of pre-operative cefazolin, cefuroxime, and cefamandole in
32 controlling the growth of pathogenic aerobic oral flora in comatose patients undergoing
33 neurosurgical procedures was investigated.

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35 At the time of induction of general anaesthesia for neurosurgical procedure, 10, 11,
36 and 9 comatose patients (Glasgow coma scale < 7) received 1 g of cefazolin, 1.5 g of
37 cefuroxime, or 2 g of cefamandole intravenously, respectively. Clinical data are detailed in
38 Table 1. At the completion of the surgical procedure, saliva samples were obtained from
39 above the cuff of the endotracheal tube and residual serum samples from routine blood testing
40 were simultaneously collected by procedures that were approved by the Ethical Committee of
41 the University of Debrecen. The actual antibiotic concentrations in the serum and saliva
42 samples were determined by capillary electrophoresis (CE; method detailed previously:
43 Andrasi *et al.*, 2007). The bacteria from the saliva were isolated, and the minimal inhibitory
44 concentrations (MIC) of the cephalosporins against the specific bacteria were evaluated by the
45 standard broth microdilution method according to the guidelines of CLSI (Clinical and
46 Laboratory Standards Institute, 2005).

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48 Twenty-one bacteria were isolated from the saliva in patients who received 1 g of
49 cefazolin prior to surgery. The MIC values of only 3 bacteria (*Acinetobacter baumannii*,
50 *Citrobacter freundii*, and *Pseudomonas aeruginosa*) were higher than the mean drug
51 concentrations in the serum (68.4 ± 14.4 mg/l), but the MIC values of 16 bacteria exceeded
52 the level of cefazolin in the saliva (< 0.5 mg/l). The concentration of antibiotic is given as the
53 mean \pm standard deviation (SD).

54 Twenty bacterial species were isolated from the saliva of patients who received 1.5 g
55 of cefazolin prophylactically. Two bacteria (*Citrobacter freundii* and *Pseudomonas*
56 *aeruginosa*) had higher MIC values than the mean antibiotic level in the serum (50.3 ± 18.2
57 mg/l). The concentration of cefuroxime in the saliva (< 0.5 mg/l) remained less than the MIC
58 values of 15 bacteria.

59 In the patients who received 2 g of cefamandole, 24 bacteria were isolated from the
60 saliva. Four bacteria (*Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*,
61 and *Pseudomonas aeruginosa*) had higher MIC values than the mean drug level in the serum
62 (42.4 ± 9.9 mg/l). The MIC values of 18 bacteria exceeded the levels of cefamandole in the
63 saliva (< 0.5 mg/l).

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65 Aspiration of oral bacteria is one of the main etiologic factors in developing
66 pneumonia in hospitals. During lengthy surgical procedures, saliva accumulates in the
67 pharynx above the cuff of the tube used for endotracheal anaesthesia. Such secretions are
68 periodically suctioned out, but this procedure cannot always be completely executed. The risk
69 for post-operative aspiration is especially high in comatose patients because of the impaired
70 function of the lower cranial nerves, resulting in impaired pharyngeal and coughing reflexes
71 that also increase the chance of developing pneumonia (Morgan & Mackay, 1999 and
72 Rosenstock *et al.*, 2001).

73 Since aspiration of pathogenic oral flora increases the incidence of pneumonia,
74 administration of prophylactic antibiotics in high-risk patients is of enormous clinical
75 importance (Kraus *et al.*, 2005). In this study, the efficacy of prophylactic cefazolin,
76 cefuroxime, and cefamandole in controlling the growth of oral pathogenic bacteria was
77 evaluated by monitoring the actual concentrations of antibiotics in the serum and saliva. The
78 detected drug levels in the serum proved to have a significant effect against bacteria isolated
79 from the saliva, but the concentrations of every cephalosporin tested was very low in the
80 saliva; cefazolin, cefuroxime, and cefamandole did not reach the MIC values of 76.2%, 75%,
81 and 75% of the bacteria, respectively, and therefore had only a very moderate effect on the
82 oral flora, and thus the potential prevention of aspiration pneumonia.

83 Direct monitoring of the effectiveness of antibiotics is not yet included in any clinical
84 practice, although many previous analyses have called attention to very different penetration
85 rates of antibiotics in different secretions. These observations are particularly important for
86 patients in whom bacterial diseases can develop by means of a secretion. During recent
87 investigations CE has been applied and shown to be an inexpensive, simple, and creditable
88 method that requires very small samples and offers the opportunity for clinicians to evaluate
89 the actual efficacy of antibiotics for promoting optimisation of individual antibiotic therapies.

90 In the case of patients at high-risk for the aspiration of pathogenic oral flora, e.g., in
91 comatose patients, in place of cefazolin, cefuroxime, and cefamandole, a prophylactic
92 antibiotic should be administered that is able to reach the MIC values of the majority of
93 pathogenic bacteria in the saliva. Determination of the MIC values of the bacteria isolated
94 from the saliva collected during the surgical procedure can facilitate specific antibiotic
95 therapy in the case of post-operative aspiration pneumonia.

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125 **Table 1.** Clinical parameters of patients

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	Cefazolin	Cefuroxime	Cefamandole
128 Number of cases:	10	11	9
129 Age (years):	53.5 ± 12.3	49.2 ± 11.5	46.9 ± 11.5
130 Gender (female/male):	5/5	4/7	5/4
131 Body weight (kg):	72.0 ± 15.2	71.1 ± 12.0	69.3 ± 12.7
132 Duration of surgery (min):	133.5 ± 19.5	125.5 ± 23.7	120.4 ± 24.3