Letters to the Editor

Colonization Resistance: A Guide to Antibiotic Policy in the ICU

To the Editor:

In leukopenia caused by chemotherapy, long-term prophylaxis of infection with gram-negative rods is possible by using several different antibiotic regimens.[1] This concept was also applied, with remarkable results, to infection prophylaxis in artificially ventilated patients.[2] Recently we modified the regimen so that it costs no more than NLG 15 (US $6.45) per day.[1] Our regimen attempts to decontaminate the colonized (mouth) and potentially colonized (stomach) body sites locally and to use systemic prophylaxis. The decontamination is mainly concerned with gram-negative rods and yeast, and is called selective decontamination (SD) because the antimicrobial agents used do not affect colonization resistance.[1]

We expected that elimination of potentially pathogenic microorganisms from the colonized areas would drastically reduce respiratory infections in artificially ventilated patients. This hypothesis was tested by analysis of ongoing surveillance data.

The data were collected during seven periods (1-7), each covering six months, from June 1, 1982 through November 30, 1985. Surveillance was carried out prospectively. An infection control nurse (ICN) daily recorded temperature and other signs indicating infection, antibiotic use, and any surgical procedures of all eligible patients. A culture of sputum or tracheal secretion, urine, and wounds was initiated twice a week. All patients were monitored for three days following discharge from the ICU.

The selective decontamination regimen consisted of the following:

a) an oral paste (SD paste) composed of amphotericin B 2%, colistin sulfate 2%, norfloxacin 2% in hydroxypropyl-methylcellulose (4,000 cp 20% in white petrolatum); 1 g qid
b) amphotericin B suspension 10% (Fungizone®, Squibb); 5 mL qid
c) SD powder containing sulfalene 50 mg (sulfamethoxypyrazine), trimethoprim 125 mg, norfloxacin 50 mg; 1 powder qid

As a rule *b* and *c* were administered by nasogastric tube, but they could also be administered orally. In case of renal impairment or allergy to sulfonamides, the sulfalene was replaced by colistin sulfate (100 mg), and in case of leukopenia the SD powder was

TABLE 1
MORTALITY, ANTIBIOTIC PROPHYLAXIS (SD), AND ANTIBIOTIC THERAPY IN VENTILATED ICU PATIENTS

	Periods							
Patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**All**
Total number	28	29	28	37	32	35	50	239
Died	12	8	8	6	8	5	17	64
SD only	—	—	—	—	7	3	13	23
SD + antibiotic	—	—	—	—	16	26	27	69
Antibiotic therapy with:	23	23	22	29	22	28	33	180
penicillin	4	4	4	1	2	—	2	17
ampicillin*	16	15	5	2	1	—	—	39
azlocillin	2	1	1	1	1	—	3	9
dicloxacillin	4	2	5	—	1	1	1	14
cefuroxime	—	—	—	—	—	1	4	5
cefotaxime	—	4	4	12	13	12	14	59
tobramycin	4	4	4	13	14	13	11	63
metronidazole	5	4	7	12	16	15	12	71
co-trimoxazole†	7	2	12	15	5	11	13	65
other‡	—	3	2	—	2	3	4	14
Total antibiotics	42	39	44	56	55	56	64	356

* *Including amoxicillin.*
† *Including trimethoprim.*
‡ *Clindamycin, doxycycline, erythromycin, and rifampin.*

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TABLE 2
HOSPITAL INFECTIONS IN PATIENTS ARTIFICIALLY VENTILATED*

Patients			Infections by Localization				
Period	Total	Infected (%)	Urine	Wound	Septicemia	Airway	Total
1	28	21 (75)	5	7	5	16	33
2	29	15 (52)	8	5	2	13	28
3	28	19 (68)	7	8	3	14	32
4	38	18 (47)	5	5	2	14	26
5	32	15 (47)	3	4	1	11	19
6	35	14 (40)	4	3	0	7	14
7	50	15 (30)	5	6	0	9	20
	240†	117 (49)	37	38	13	84	172
Test for trend, *P* value:		<0.0001	0.029	0.029	0.0003	<0.0001	NA

* *The fraction of patients with one or more infections decreased significantly, which is mainly due to a lower incidence of respiratory tract infections and septicemia.*
† *Test for goodness of fit, uniform distribution:* P=*0.09.*
NA = Not applicable.

replaced by oral tobramycin and colistin.[2]

In the various periods, age, duration of stay, and duration of ventilation were compared by means of Kruskal and Wallis' H test and a k sample trend test.[3] The relative frequency of the infections was tested with van Eeden's test for trend among k probabilities.[4] The chi-square test was used for the other tests. There were no significant differences—in age (median 61), duration of stay (median 7), and duration of ventilation (median 3)—between the groups of patients receiving artificial ventilation.

During the first two periods, penicillins were the most frequently used antibiotics (Table 1). In period 3, this place was taken by co-trimoxazole. In the last four periods penicillins were replaced by a combination of cefotaxime, tobramycin, and metronidazole in case of (postperforation) peritonitis, or co-trimoxazole in case of less severe conditions. No significant difference for mortality was found for the observation period as a whole ($P = 0.16$). The percentage of patients with one or more hospital infections was high: 117 out of 240 (49%, Table 2). This percentage gradually dropped over the seven periods (from 21 of 28 [75%] to 15 of 50 [30%], $P < 0.0001$, van Eeden's test for trend). This drop mainly related to respiratory infections (from 16 of 28 [57%] to 9 of 50 [18%], $P < 0.0001$) and to the small but clinically important group of septicemia/bacteremia patients (from 5 of 28 [18%] to 0 of 50, $P = 0.0003$). However, the number of urinary tract infections and wound infections also dropped significantly ($P = 0.029$ in both cases). Enterobacteriaceae chiefly accounted for the drop (from 33 to 4). The number of hospital infections caused by *Pseudomonas* also fell (from 10 to 3). The infections caused by *Candida* and other yeast infections occurred more frequently in periods 3 and 4 than in the previous and subsequent periods (21 of 66 [32%] *v* 15 of 174 [9%], $P<0.0001$, chi-square test). That may be related to the increased use of co-trimoxazole, which seems to promote yeast infections,[1] and which later was compensated for by administering antimycotic amphotericin B as a part of SD. At the time of the study we did not yet apply a severity of disease classification (ie, APACHE [5]). Therefore the improved mortality rate during the first six periods could not be evaluated objectively. Nor could we separate mortality due to infections and other causes.

We conclude that the concept of colonization resistance may be important as a guide to antibiotic policy in the ICU. We hope that our study invites controlled studies of similar antibiotic regimens.

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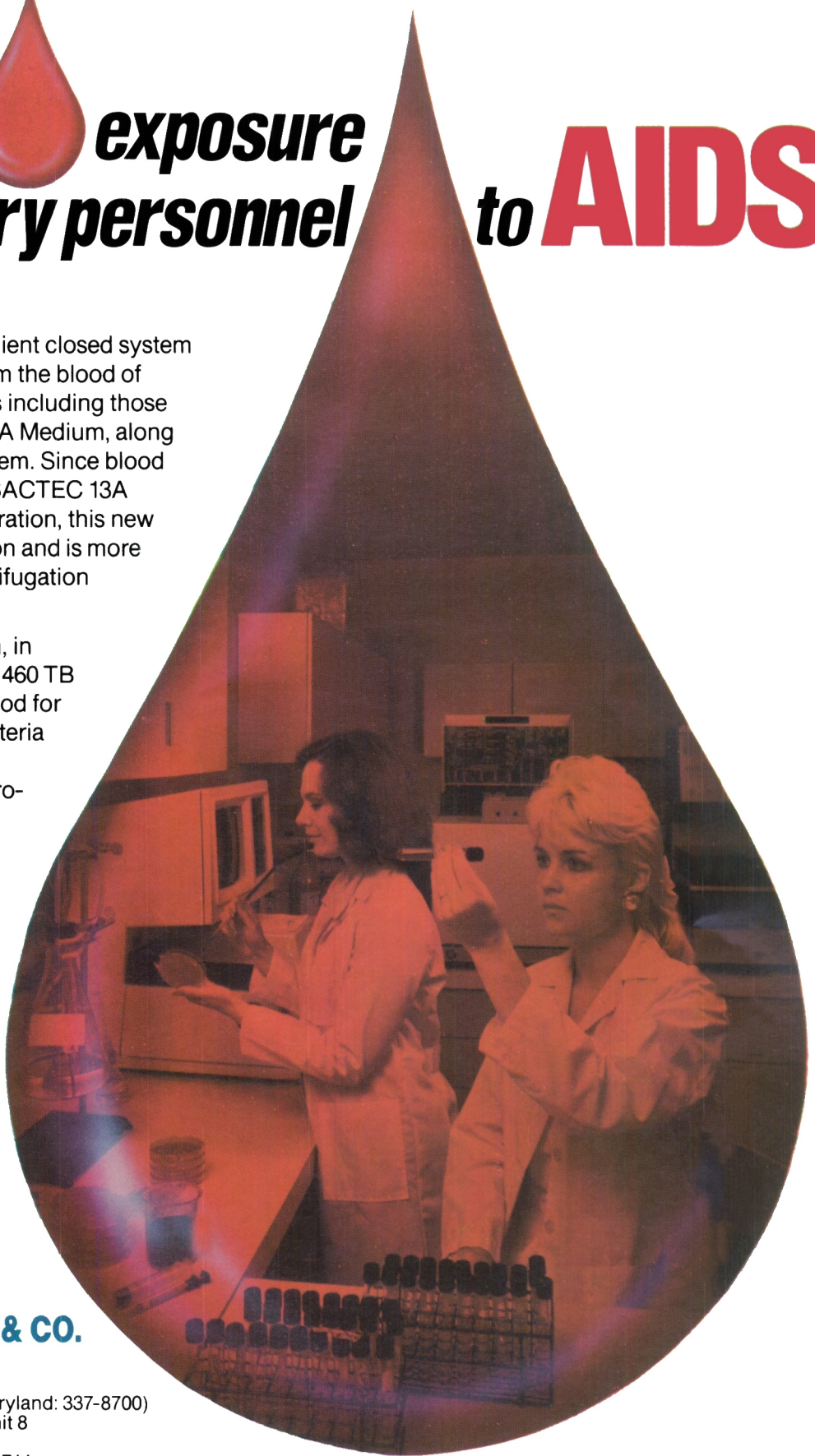

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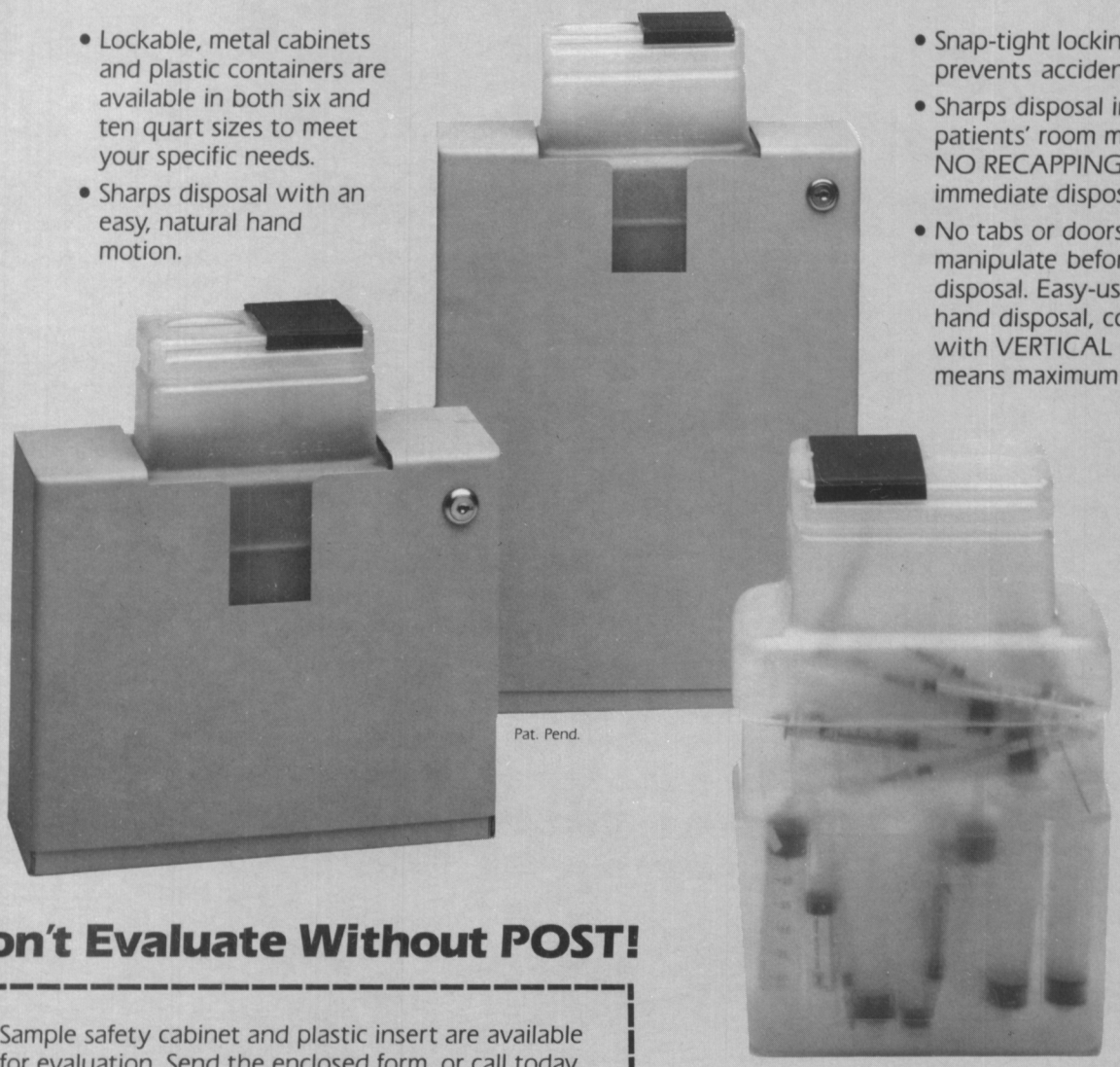

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