Survival Benefit in Critically Ill Burned Patients Receiving Selective Decontamination of the Digestive Tract

A Randomized, Placebo-Controlled, Double-Blind Trial

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Objective: To evaluate whether selective digestive decontamination (SDD) reduces mortality from any cause, and the incidence of pneumonia among patients with severe burns.

Summary Background Data: SDD is a prophylactic strategy to reduce infectious morbidity and mortality in critically ill patients. Two meta-analyses and a recent randomized controlled trial demonstrated a mortality reduction varying between 20% and 40%. But this technique has never been properly evaluated in severely burned patients.

Methods: The design of this single-center trial was randomized, double blind, placebo controlled. Patients with burns ≥20% of total body surface and/or suspected inhalation injury were enrolled and assigned to receive SDD or placebo for the total duration of treatment in the burn intensive care unit (ICU).

Results: One hundred seventeen patients were randomized and 107 were analyzed (53 in the SDD group and 54 in the placebo group). The ICU mortality was 27.8% in the placebo group and 9.4% in the SDD group in the burn ICU. Treatment with SDD was associated with a significant reduction in mortality both in the burn ICU (risk ratio 0.25; 95% CI 0.08 to 0.76) and in the hospital (risk ratio 0.28; 95% CI 0.10 to 0.80), following adjustment for predicted mortality. The incidence of pneumonia was significantly higher in the placebo group: 30.8 and 17.0 pneumonias per 1000 ventilation days ($P = 0.03$) in placebo and SDD group, respectively.

Conclusions: Treatment with SDD reduces mortality and pneumonia incidence in patients with severe burns.

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Pneumonia has been shown to be a risk factor for mortality in patients with severe burns.[1,2] The expected increase in mortality due to pneumonia has been estimated to be 25% in a retrospective cohort study.[1] A prospective study showed that endogenous pneumonia due to microorganisms carried by the burn patients in the admission flora is associated with mortality.[2]

Selective digestive decontamination (SDD) is a technique that protects critically ill patients from pneumonia and from dying. The most recent meta-analysis of randomized trials in medical/surgical patients showed a reduction in pneumonia and mortality rates: odds ratio 0.35 (95% CI 0.29 to 0.41) and 0.78 (95% CI 0.68 to 0.89), respectively.[3] The meta-analysis in surgical patients demonstrated an even greater marked treatment effect: odds ratio 0.19 (95% CI 0.15 to 0.26) and 0.70 (95% CI 0.52 to 0.93) for pneumonia and mortality, respectively.[4] A recent randomized trial of 934 patients confirmed the survival benefit of SDD with a relative risk reduction of 35% in ICU and of 22% in hospital mortality and a decrease in colonization caused by resistant aerobic Gram-negative bacilli (AGNB).[5]

The efficacy of SDD has been evaluated in severely burned patients in 1 prospective and in 1 historically controlled trial.[6,7] Jarrett et al[6] studied prospectively SDD using neomycin, erythromycin, nystatin in 20 severely burned patients, comparing them with 10 control patients with burns of an average of 44% body surface area. All patients were treated in a laminar flow unit. Infections were halved in the SDD group as there were 11 infections in both treated and control patients. There were no deaths in either group.

Mackie at al[7] described a series of 31 consecutive patients with burns of greater than 30% of total body surface area who were treated with SDD, comparing them with 33 consecutive historic controls. The incidence of respiratory tract infections (27.3% versus 6.5%) and mortality (21.2 versus 3.2%) were reduced in the SDD group.

We report the results of the first randomized placebo-controlled trial in severely burned patients with 2 end points: mortality and endogenous pneumonia.

PATIENTS AND METHODS

Patients

All patients ≥14 years old with burns of ≥20% of total body surface area and/or suspected inhalation injury and an interval between injury and burn ICU admission ≤3 days were eligible. Exclusion criteria were a stay in the burn ICU <3 days, withdrawal of treatment within 3 days, immunosuppression, pregnancy, and inhalation injury not requiring mechanical ventilation within the first 3 days.

Setting

This study was conducted in a 6-bed burn ICU of a tertiary hospital between May 1, 1997, and January 31, 2000. The annual admission rate was 80 burn patients.

Management of Burn Patients

Patients were resuscitated using the modified Parkland formula.[8] Enteral nutrition was started within the 24 hours of injury and gradually increased during the first 3 days. All patients received a diet supplemented with ω-3-acids, nucleotides and arginine, (Perative, Abbott). Nutritional requirements were empirically estimated according to the Harris-Benedict formula using a stress factor from 1.5 to 2. Protein support was between 1.5 a 2.0 g/kg/d.

Excision and graft of the burn wound usually began within the first 2 days. Burn wounds were treated with closed dressings and daily application of silver sulfadiazine or iodine-povidone ointment.

Inhalation injury was suspected in patients with facial and neck injuries and in patients who suffered burns in an enclosed space. All suspected patients underwent bronchoscopy. The diagnosis of inhalation injury was made by demonstration of inflammatory changes in the respiratory tract.

Infection Control Methods

The isolation practices implemented in the burn ICU included hand decontamination before each patient contact, washing hands and changing gloves between sequences of care, and wearing gloves in case of contact with burn wound body substances.[9]

Antibiotic Policy

Systemic antibiotics, cefotaxime plus an aminoglycoside, were administered empirically when clinical signs of infection developed and were adjusted according to the microbiologic results. Infections owing to Gram-positive bacteria were treated with a β-lactam. Burn patients with an AGNB infection received a combination of cefotaxime and an aminoglycoside. Cefotaxime was replaced by ceftazidime when the infection was due to *Pseudomonas aeruginosa*. Systemic vancomycin was given when the infection was caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

No antibiotic prophylaxis was given before surgical wound excision and grafting.

Study Intervention

SDD included (i) intravenous administration of cefotaxime (1 g q 8 hours) for 4 days; (ii) topical application in the oropharynx using nonabsorbable polymyxin E, tobramycin and amphotericin B 0.5 g of a 2% paste qid; (iii) digestive administration of a 10-mL solution containing 100 mg of polymyxin E, 100 mg of tobramycin, and 500 mg of amphotericin B qid; (iv) surveillance samples of throat and rectum on admission and twice a week.

The control patients received isotonic 0.9% saline i.v. The placebo paste and the digestive solution were indistinguishable from the test medication with regard to color, smell, and consistency. Both control and test medication was prepared in the Department of Pharmacy of the hospital.

Study Design

The study was a prospective, randomized, double-blind, placebo-controlled trial. The patients were stratified according to the suspicion of inhalation injury. The result of randomization was introduced in a sealed envelope that was kept in the Department of Pharmacy. The hospital pharmacist was the only person to be informed about the identity of the study medication.

The study was approved by the Institutional Board for Clinical Research. Informed consent was obtained from the patient or the relatives.

Microbiology

Surveillance samples of throat and rectum were processed using previously described methods.[2,10]

Surface wound samples were obtained on admission and twice weekly afterward.

Diagnostic samples of tracheal aspirates, blood, and urine were taken on clinical indication only to microbiologically confirm the clinical diagnosis of infection. Standard microbiologic techniques were used.[11]

Definitions

Pneumonia was defined as the presence of new (or progressive) pulmonary infiltrates persisting for more than 48 hours on chest x-ray, in addition to at least 2 of the following criteria: (i) fever ≥38.5°C or hypothermia <35.0°C; (ii)

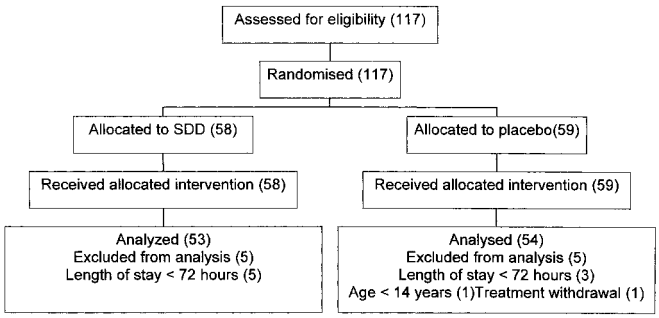

FIGURE 1. Study Flow Chart.

leukocytosis $\geq$10,000/mm^3 or leukopaenia $<$3000/mm^3[11]; (iii) isolation of potential pathogens in high concentration of $\geq$4+ [10^7 colony forming units/mL] using semiquantitative culture, from unprotected purulent tracheal aspirates.[12–14]

The diagnosis of pneumonia was made by 1 intensivist (EC) and 1 radiologist (DGS) not involved in the patient care and who were blinded to the treatment assignment.

Urinary tract infections and bloodstream infections were diagnosed according to CDC definitions for nosocomial infections.[12] Burn wound infections were classified according to the classification proposed by the Peck et al.[15]

Infections were classified[16] as primary endogenous when they were caused by microorganisms that were carried in throat and/or gut upon admission to the ICU, secondary endogenous when they were caused by microorganisms not carried on admission but acquired in throat and gut later during the treatment in the ICU, and exogenous when they were caused by microorganisms that were never present in throat and rectal swabs.

Sample Size Calculations

The sample size was calculated aiming for a 60% reduction in the incidence of pneumonia incidence from 48% in the placebo group[2] to 20% in the SDD group, with a 2-tailed α-level of 0.05 and a power of 80%. The calculation deemed 102 patients were required for the study.

Statistical Analysis

Descriptive statistics were expressed as proportions, mean, standard deviation, median, and interquartile range (IQR), as indicated. Incidence of infection was defined as the number of infections per 1000 device-days or 1000 patient-days.

The comparison of baseline variables and infections was performed using Wilcoxon test for continuous variables and the χ^2 test or Fisher exact test when appropriate for discrete variables. Mortality was plotted as Kaplan-Meier curves that were compared with the log-rank test. The Cox proportional hazards regression model was used for adjusting the relative risk of mortality for the predicted mortality estimated according to the Smith et al[17] model.

RESULTS

Demographics

A total of 117 patients were eligible within the study period; 10 patients were excluded after enrollment (5 in each group) (Fig. 1). Five patients who were assigned to receive SDD were excluded from the analysis because they were discharged within 72 hours. Three patients in the placebo group were not included in the analysis because they stayed $<$72 hours in the burn ICU, 1 patient was $<$14 years old, and the treatment was withdrawn in the fifth placebo patient. In total, 107 patients were analyzed, 53 received SDD, and 54 received placebo. The analysis was considered to be by intention to treat because all 10 excluded patients did not fulfill the inclusion criteria of the trial.

The 2 groups were similar with respect to sex, age, total burn area, full-thickness burn area, and inhalation injury (Table 1). There was no difference in patients requiring ventilation and in the number of ventilator days required by

TABLE 1. Demographics

	Placebo, N = 54	SDD, N = 53	*P*
Age, y, mean (SD)	48.1 (18.5)	41.4 (17.7)	0.06
Sex (male)	40 (74%)	44 (83%)	0.35
Body surface burn, mean (SD)	37.7 (21.1)	34.0 (21.4)	0.25
Full-thickness burn, mean (SD)	19.0 (18.8)	19.3 (15.3)	0.59
Inhalation injury	37 (68%)	34 (64%)	0.68
Mechanical ventilation	43 (80%)	39 (74%)	0.50
Days of mechanical ventilation of survivors, mean (SD)	33.6 (24.3)	30.1 (35.4)	0.10
Predicted ICU Mortality,[16] mean (SD)	33.1 (20.2)	24.7 (19.4)	0.09
ICU length of stay of survivors, mean (SD)	33.6 (24.5)	30.6 (30.9)	0.58
Hospital length of stay of survivors, mean (SD)	52.3 (26.3)	50.6 (45.5)	0.84

the survivors. Among the survivors, the length of stay neither in the burn ICU nor in the hospital was different.

Mortality

There were fewer fatalities among patients receiving SDD compared with control: 5 versus 15 (9.5% versus 27.8%); risk ratio 0.33 (95% CI 0.13 to 0.85) during treatment in the burn ICU. Five placebo patients died in the first week, 6 in the second week, and 4 died later on during their stay in ICU. In the SDD group, 2 patients died in the second week and the other 3 succumbed after the third week. Figure 2 shows the Kaplan-Meier curves of the probability of survival over time of patients receiving SDD or placebo. When adjusting mortality for the predicted mortality using the Cox regression model, the risk ratio was 0.25 (95% CI 0.08 to 0.76).

One patient who received SDD died in the ward following discharge from the burn ICU, while there were no extra deaths in the placebo group (6 versus 15). The risk ratio of hospital mortality after adjusting for the predicted mortality was 0.28 (95% CI 0.10 to 0.80). Five patients needed to be treated with SDD to save a life.

Infections

Of the 54 placebo patients, 40 (74%) developed at least 1 infection, while 25 (43%) receiving SDD were infected ($P = 0.01$).

Forty-four patients developed a total of 58 episodes of pneumonia (Table 2). The incidence was significantly higher in the placebo group; 30.8 per 1000 ventilator-days versus 17.0 ($P = 0.03$). Primary endogenous pneumonias were completely prevented using SDD, while there were 17 primary endogenous pneumonias in the placebo group, mainly due to *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. There was no difference in the incidence of secondary endogenous pneumonia, which was invariably caused by MRSA and AGNB. The median time of onset of primary endogenous pneumonias was 3 days (IQR 3, 6), while the secondary endogenous pneumonias occurred after 2 weeks, median 17 days (IQR 14, 31.5).

TABLE 2. Pneumonias

	Placebo, N = 54	SDD, N = 53
Number of patients with pneumonia	26 (48%)	18 (34%)
Number of pneumonias	36	22
Primary endogenous	17	0
Secondary endogenous	16	17
Exogenous	3	5
Rates of pneumonia (per 1000 d of mechanical ventilation)*	30.8	17.0*
Primary endogenous		
S aureus	10	
H influenzae	10	
S pneumoniae	8	
K pneumoniae	2	
E coli	2	
M morganii	1	
Secondary endogenous		
MRSA	6	11
P aeruginosa	7	2
Acinetobacter sp	5	5
M morganii	–	1
P mirabilis	1	–
E coli	1	–
S paucimobilis		1
Exogenous		
MRSA	–	1
P aeruginosa	–	3
Acinetobacter sp	–	1
S paucimobilis	1	1
S maltophillia	2	1
E cloacae		–

*$P = 0.03$.

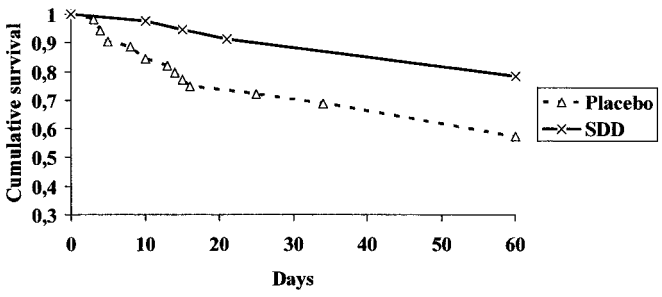

FIGURE 2. Kaplan-Meier estimates of survival of patients included in the trial.

Of the 53 patients receiving SDD, 19 (36%) developed 36 bloodstream infections while 17 of 54 (31%) placebo patients developed 23 ($P = 0.6$) (Table 3). The incidence was 20.7 per 1000 days in the treated patients versus 15.0 in the placebo patients. Primary endogenous infections of the bloodstream were uncommon and mainly due to low-level pathogens, coagulase-negative staphylococci, and enterococci. Again, MRSA and AGNB caused secondary endogenous infections of the blood in both groups. The median time of onset of primary endogenous and secondary endogenous bloodstream infections was 13.5 days (IQR 7.25, 37.25) and 24.5 (IQR 13.25, 48), respectively.

TABLE 3. Bloodstream Infections

	Placebo, N = 54	SDD, N = 53
Number of patients with bloodstream infections	17 (31%)	19 (36%)
Number of bloodstream infections	23	36
Primary endogenous	7	11
Secondary endogenous	15	23
Exogenous	1	2
Rates of bloodstream infections (per 1000 d)	15.0	20.7
Primary endogenous		
E faecalis	2	1
Coagulase–negative staphylococci	2	7
S aureus	1	1
E faecium	–	1
E coli	1	–
P aeruginosa	1	–
Anaerobes	–	1
Secondary endogenous		
MRSA	5	13
P aeruginosa	6	9
Acinetobacter sp	3	6
E faecium	1	2
E coli	3	–
E cloacae	3	–
K pneumoniae	1	–
Exogenous		
E faecium	1	–
E cloacae	–	1
C parapsilosis	–	1

Six patients (11%) in the treated group developed 8 urinary tract infections; 14 patients (26%) developed 17 urinary tract infections in the placebo group. The incidence was 4.6 per 1000 bladder-catheter days versus 11.1, respectively ($P = 0.04$). This reduction is observed in the primary endogenous infections, 1 in the SDD group and 12 in the placebo group, mainly caused by *Escherichia coli* and enterococci. The median time of onset of primary endogenous and secondary endogenous urinary tract infections was 6 days (IQR 4, 13) and 50 (IQR 23.25, 88,25).

Ten patients in the treated group (19%) and 11 patients in the placebo group (20%) developed 13 and 11 burn-wound infections, respectively. The burn-wound infection rates were 7.5 per 1000 days in the SDD group and 7.2 in the placebo group. Primary endogenous infections were uncommon in both groups. Secondary endogenous infections caused by MRSA and AGNB occurred at a median of 20.1 day (IQR 12; 48.5).

DISCUSSION

Four findings emerge from this randomized controlled trial: (i) a reduction in mortality of 57% in the burn ICU and 50% in hospital mortality; (ii) a reduction in primary endogenous infections, pneumonias, and urinary tract infections due to community bacteria; (iii) there was no difference in the incidence of secondary endogenous infections due to hospital bacteria including MRSA and AGNB; (iv) a trend towards an increase in MRSA infections was observed.

The mortality in the control group was 27.8%. This is in line with mortality in patient populations, with an incidence of inhalation injury of 66%, an incidence of mechanical ventilation of 77%, a mean age of 45 years, and a mean body surface area burned of 36%.[1,2,18] The treatment with SDD significantly reduced mortality both in the burn ICU and in the hospital. The survival benefit was mainly established within the first 10 days.

The assessed intervention prevented primary endogenous pneumonia due to community bacteria. This type of infection has been shown to be associated with death in severely burned patients with inhalation injury.[2] The 17 primary endogenous pneumonias in the control group were immediately treated with adequate antimicrobials on the day of diagnosis, ie, day 3. Whether the delay of 3 days in antibiotic treatment in burn patients with inhalation injury caused an early difference in mortality difference is compelling. Several studies in critically ill patients with pneumonia that evaluated outcome following antibiotic therapy in pneumonia show that a delay in the administration of adequate antibiotic treatment increased mortality.[19,20]

Secondary endogenous infections occurred late, ie, 2 weeks after admission to the burn ICU. There was no difference in the incidence of this type of infection for lungs, blood, bladder, and burn wounds; 35.2% of the control patients had AGNB infections, while 26.4% of the patients receiving prophylaxis. These data reflect the failure of the enteral antimicrobials polymyxin E/tobramycin in about 25% of this patient population. The type of patient at risk for wound colonization with AGNB, particularly *P. aeruginosa*, the presence of external AGNB sources in the environment, and the sporadic episodes of ileus induced by opioids may explain the partial failure in eradicating AGNB from the digestive tract.[21]

By design, SDD using polymyxin E/tobramycin/amphotericin B does not cover MRSA. Fourteen SDD patients (26.4%) developed MRSA infections, while the incidence of MRSA infection in the control group was 20%. MRSA was endemic in the burn ICU throughout the trial. Trial patients represented 40% of all burn patients admitted to the burn ICU. Both treated and control groups were exposed to

MRSA. The trend to a higher infection rate in patients receiving SDD suggests that polymyxin/tobramycin/amphotericin B selects MRSA. This finding is in line with other trials of SDD in ICU with ongoing MRSA endemicity.[22–27] The addition of 4% vancomycin to the oropharyngeal paste combined with 500 mg qid of enteral vancomycin has been reported to control outbreak and endemicity due to MRSA[28,29] without harmful side effects such as the emergence of vancomycin-resistant enterococci.

The most recent randomized controlled trial with end point of carriage of resistant AGNB in a surgical/medical ICU free from MRSA and vancomycin resistant enteroccci demonstrated significantly fewer carriers in the SDD group compared with the control group (16 versus 26: $P < 0.0001$).[5] Concerns about antimicrobial resistant are justified in burn ICU[30] using SDD or not. Hence, we recommend careful monitoring of carriage of resistant bacteria using regular surveillance samples.

The major strength of this study is the proper design and the largest sample size ever reported in a randomized clinical trial in this population. A small trial of 23 burn children receiving only the enteral solution of SDD reported no difference in mortality and morbidity.[31]

The results of this study in adult burn patients show that the immediate administration of parenteral cefotaxime and intestinal nonabsorbable antibiotics contributes to the reduction of mortality in severely burned patients, with a high proportion of patients with inhalation injury and requiring mechanical ventilation. Whether the prevention of primary endogenous infections by the parenteral cefotaxime component only reduces the mortality to the same extent as the full SDD protocol can only be answered in a randomized trial in which parenteral cefotaxime is compared with cefotaxime plus enteral nonabsorbable antibiotics.

All burn patients who are admitted to our ICU and who fulfill the inclusion criteria of this trial currently received the SDD protocol plus topical vancomycin since the analysis of this randomized trial. The mortality rate is 12.8%.

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REFERENCES

1. Shirani KZ, Pruitt BA, Mason AD. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205:83–87.
2. de la Cal MA, Cerdá E, García-Hierro P, et al. Pneumonia in patients with severe burns: a classification according to the concept of the carrier state. *Chest*. 2001;119:1160–1165.
3. Liberati A, D'Amico R, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd; 2004.
4. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. *Arch Surg*. 1999;134:170–176.
5. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*. 2003; 362:1011–1016.
6. Jarrett F, Balish E, Moylan JA, et al. Clinical experience with prophylactic antibiotic bowel suppression in burn patients. *Surgery*. 1978;83: 523–527.
7. Mackie DP, van Hertum WA, Schumburg T, et al. Prevention of infection in burns: preliminary experience with selective decontamination of the digestive tract in patients with extensive injuries. *J Trauma*. 1992;32:570–575.
8. Baxter CR. Fluid volume and electrolyte changes of the early post-burn period. *Clin Plast Surg*. 1974;1:693–709.
9. Lee JJ, Marvin JA, Heimbach DM, et al. Infection control in a burns center. *J Burn Care Rehabil*. 1990;11:575–580.
10. Leonard EM, van Saene HK, Shears P, et al. Pathogenesis of colonisation and infection in a neonatal surgical unit. *Crit Care Med*. 1990;18: 264–269.
11. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing: NCCLS Approved Standard M100-S9*. Wayne: National Committee for Clinical Laboratory Standards; 1999.
12. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. *Am J Infect Control*. 1988;16:128–140.
13. Niederman MS, Torres A, Summer W. Invasive diagnostic testing is not needed routinely to manage suspected ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 1994;150:565–569.
14. Ruiz M, Torres T, Ewig S, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med*. 2000;162:119–125.
15. Peck MD, Weber J, McManus A, et al. Surveillance of burn wound infections: a proposal for definitions. *J Burn Care Rehabil*. 1998;19: 386–389.
16. van Saene HK, Damjanovic V, Murray AE, et al. How to classify infections in intensive care units: the carrier state, a criterion whose time has come. *J Hosp Infect*. 1996;33:1–12.
17. Smith DL, Cairns BA, Ramadan F, et al. Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients. *J Trauma*. 1994;37:655–659.
18. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med*. 1998;338:362–366.
19. Alvarez-Lerma F, ICU-Acquired Pneumonia Study Group. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. *Intensive Care Med*. 1996;22:387–394.
20. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest*. 1997; 111:676–685.
21. Tetteroo GWM, Wagenvoort JHT, Bruining HA. Bacteriology of selective decontamination: efficacy and rebound colonization. *J Antimicrobiol Chemother*. 1994;34:139–148.
22. Gastinne H, Wolff M, Delatour F, et al. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics: the French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med*. 1992;326:594–599.
23. Hammond JM, Potgieter PD, Saunders GL, et al. Double-blind study of selective decontamination of the digestive tract in intensive care. *Lancet*. 1992;340:5–9.
24. Ferrer M, Torres A, Gonzalez J. , et al. Utility of selective digestive decontamination in mechanically ventilated patients. *Ann Intern Med*. 1994;120:389–395.
25. Verwaest C, Verhaegen J, Ferdinande P. , et al. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med*. 1997;25:63–71.
26. Wiener J, Itokazu G, Nathan C, et al. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995;20:861–867.

27. Lingnau W, Berger J, Javorsky F, et al. Selective intestinal decontamination in multiple trauma patients: prospective, controlled trial. *J Trauma*. 1997;42:687–694.
28. de la Cal MA, Cerdá E, van Saene HKF. et al. Effectiveness and safety of oral vancomycin to control endemicity of methicillin-resistant *Staphylococcus aureus* in a medical/surgical intensive care unit. *J Hosp Infect*. 2004;56:175–183.
29. Silvestri L, Milanese M, Oblach L, et al. Enteral vancomycin to control methicillin-resistant *Staphylococcus aureus* outbreak in mechanically ventilated patients. *Am J Infect Control*. 2002;30:391–399.
30. Edwards-Jones V, Greenwood JE, Manchester Burns Research Group. What's new in burn microbiology? James Laing Memorial Prize Essay 2000. *Burns*. 2003;29:15–24.
31. Barret JP, Jeschke MG, Herndon DN. Selective decontamination of the digestive tract in severely burned pediatric patients. *Burns*. 2001;27: 439–445.