

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Darouiche RO, Wall MJ Jr, Itani KMF, et al. Chlorhexidine–alcohol versus povidone–iodine for surgical-site antisepsis. *N Engl J Med* 2010;362:18-26.

**Table 1 (full). Baseline Characteristics of Patients (Intention-to-Treat Population). \***

	<b>Chlorhexidine- Alcohol (n=409)</b>	<b>Povidone- Iodine (n=440)</b>	<b>P-Value†</b>
Male sex - %	58.9	55.9	0.40
Age - years			0.87
Mean	53.3±14.6	52.9±14.2	
Range	18 to 100	19 to 85	
Gastrointestinal disease - %	67.0	65.0	0.56
Cardiopulmonary disease - %	33.5	37.1	0.28
Gynecological disease - %	13.0	12.1	0.76
Neurologic disease - %	12.5	10.0	0.28
Renal disease - %	7.3	8.4	0.61
Immunologic disease - %	4.7	4.8	>0.99
Cancer - %	58.0	61.4	0.33
Diabetes mellitus- %	15.4	13.9	0.56
Malnutrition - %††	6.1	5.2	0.66
Liver cirrhosis - %	2.2	3.0	0.52
History of Alcohol abuse - %	17.9	19.3	0.60

**Table 1 (full). Baseline Characteristics of Patients (Intention-to-Treat Population). \***

	<b>Chlorhexidine- Alcohol (n=409)</b>	<b>Povidone- Iodine (n=440)</b>	<b>P-Value†</b>
History of smoking - %	37.2	34.6	0.43
Mechanical ventilation - %	0.2	0.5	>0.99
Documented colonization with MRSA - %	2.0	2.3	0.81
Systemic antibiotics			
Initiated preoperatively - %	100.0	100.0	>0.99
Type of antibiotics			
Cephalosporin - %	73.3	74.3	0.76
Glycopeptide - %	12	12.7	0.76
Nitroimidazole - %	9.0	9.1	>0.99
Aminoglycoside - %	7.1	10.2	0.11
Carbapenem - %	7.3	6.1	0.50
Penicillin - %	3.2	3.9	0.71
Macrolide - %	2.2	2.7	0.66
Fluoroquinolone - %	2.7	1.8	0.49

**Table 1 (full). Baseline Characteristics of Patients (Intention-to-Treat Population). \***

	<b>Chlorhexidine- Alcohol (n=409)</b>	<b>Povidone- Iodine (n=440)</b>	<b>P-Value†</b>
Monobactam - %	2.4	0.7	0.05
Tetracycline - %	0.2	0.5	>0.99
Duration of administration – days			>0.99
Mean	1.1± 1.2	1.1 ± 0.8	
Range	1 to 20	1 to 11	
Initiated postoperatively - %	51.7	48.9	0.41
Duration of surgery – hours			>0.99
Mean	3.0±1.5	3.0±1.5	
Range	0.5 to 10.0	0.3 to 12.0	
Abdominal surgery - %	72.6	70.0	0.41
Colorectal - %	45.5	43.4	0.58
Biliary - %	10.8	12.3	0.52
Small intestinal - %	10.0	7.7	0.28
Gastroesophageal - %	6.4	6.6	0.89
Non-abdominal surgery - %	27.4	30.0	0.41

<b>Table 1 (full). Baseline Characteristics of Patients (Intention-to-Treat Population). *</b>			
	<b>Chlorhexidine- Alcohol (n=409)</b>	<b>Povidone- Iodine (n=440)</b>	<b>P-Value†</b>
Thoracic - %	10.8	13.0	0.34
Gynecologic - %	10.3	9.1	0.56
Urologic - %	6.4	8.0	0.42
Preoperative shower (overall) - %	26.7	27.0	0.94
With 4% chlorhexidine gluconate - %	16.1	18.9	0.32
With 10% povidone-iodine - %	7.3	5.2	0.26
With soap bar (0.6% triclocarban) - %	3.2	3.0	>0.99
* Plus-minus values are means $\pm$ SD.			
† P-values were based on Fisher's exact test for categorical variables and Wilcoxon Rank Sum test for continuous variables.			
†† Malnutrition defined as >10% decrease in weight over 2 months.			

**Table 2. Systemic Prophylactic Antibiotics for Colorectal Surgery (Intention-to-Treat Population).**

	<b>Chlorhexidine-Alcohol</b>	<b>Povidone-Iodine</b>	
	<b>(n=186)</b>	<b>(n=191)</b>	<b>P-Value*</b>
Cephalosporin - %	64.5	67.5	0.59
Glycopeptide - %	10.2	11.0	0.87
Nitroimidazole - %	16.1	14.7	0.78
Aminoglycoside - %	14.5	17.3	0.48
Carbapenem - %	15.1	13.6	0.77
Penicillin - %	3.8	3.7	>0.99
Macrolide - %	3.2	4.2	0.79
Fluoroquinolone - %	2.7	1.6	0.50
Monobactam - %	1.1	0	0.24
Tetracycline - %	0.5	0.5	>0.99

\*P-values were based on Fisher's exact test.

**Table 3. Univariate and Multivariate Analyses of Any Surgical Site Infection (Intention-to-Treat Population).**

Factor	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P-Value*	Odds Ratio	95% CI	P-Value†
Use of chlorhexidine-alcohol (vs. povidone-iodine)	0.55	(0.36- 0.83)	0.004	0.45	(0.26- 0.78)	0.004
Abdominal surgery (vs. non-abdominal)	4.63	(2.38- 9.04)	<0.001	3.21	(1.60- 6.42)	0.001
ASA score of 4 (vs. score of 1)	15.43	(3.55-67.01)	<0.001	4.99	(0.33-74.55)	0.24
ASA score of 3 (vs. score of 1)	5.63	(1.35-23.51)	0.006	1.81	(0.15-22.15)	0.64
ASA score of 2 (vs. score of 1)	2.78	(0.62-12.47)	0.25	2.05	(0.25-16.47)	0.50
Age (per year)	1.02	(1.01- 1.03)	0.003	1.00	(0.98- 1.02)	0.78
Female sex (vs. male sex)	0.59	(0.38- 0.90)	0.02	0.87	(0.69- 1.09)	0.21
Alcohol abuse	1.11	(0.67- 1.83)	0.69	1.12	(1.05- 1.19)	<0.001
Liver cirrhosis	3.28	(1.31- 8.24)	0.02	2.14	(1.15- 3.99)	0.02
Immunologic disease	2.72	(1.32- 5.62)	0.01	1.79	(1.00- 3.22)	0.05

**Table 3. Univariate and Multivariate Analyses of Any Surgical Site Infection (Intention-to-Treat Population).**

Factor	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P-Value*	Odds Ratio	95% CI	P-Value†
Cancer	2.05	(1.31- 3.21)	0.002	1.65	(1.04- 2.64)	0.03
Diabetes mellitus	1.90	(1.16- 3.11)	0.01	1.75	(1.05- 2.92)	0.03
Malnutrition ††	3.02	(1.57- 5.84)	0.003	2.62	(1.23- 5.55)	0.01
Gastrointestinal disease	2.96	(1.75- 5.01)	<0.001	1.27	(1.00- 1.61)	0.05
Infection at another bodily site (vs. no infection)	0.92	(0.32- 2.68)	1.00	0.89	(0.50- 1.58)	0.68
Duration of surgery (per hour)	1.33	(1.17- 1.51)	<0.001	1.11	(1.02- 1.21)	0.01
Days that surgical drain was in place (per day)	1.03	(1.00- 1.06)	0.02	1.04	(1.02- 1.05)	<0.001
Preop shower with chlorhexidine (vs. no shower)	1.56	(0.57- 4.25)	0.38	0.95	(0.78- 1.15)	0.19
Preop shower with povidone-iodine (vs. no shower)	0.13	(0.02- 0.92)	0.01	0.36	(0.32- 0.39)	<0.001
Preop shower with soap (vs. no shower)	1.08	(0.65- 1.82)	0.79	0.96	(0.75- 1.21)	0.72

<b>Table 3. Univariate and Multivariate Analyses of Any Surgical Site Infection (Intention-to-Treat Population).</b>						
<b>Factor</b>	<b>Univariate Analysis</b>			<b>Multivariate Analysis</b>		
	<b>Odds</b>			<b>Odds</b>		
	<b>Ratio</b>	<b>95% CI</b>	<b>P-Value*</b>	<b>Ratio</b>	<b>95% CI</b>	<b>P-Value†</b>

\* P-values for the univariate analyses were computed with use of Fisher’s exact test for categorical variables and a logistic regression model that adjusted for hospital site as a random effect (GEE method) for continuous variables.

†P-values for the multivariate analysis were computed with use of a logistic regression model that included all terms and adjusted for hospital site as a random effect (GEE method).

†† Malnutrition defined as >10% decrease in weight over 2 months.

<b>Table 4. Microbiology of Infections with Documented Causative Pathogens According to Study Group and Type of Infection (Intention-to-Treat Population).*</b>									
<b>No. of Isolates</b>									
<b>(n=107)</b>									
<b>Organism</b>	<b>Chlorhexidine-Alcohol</b>				<b>Povidone-Iodine</b>				<b>Both</b>
	<b>Type of Infection</b>								
	<b>Superficial</b>	<b>Deep</b>	<b>Organ-</b>		<b>Superficial</b>	<b>Deep</b>	<b>Organ-</b>		
	<b>Incisional</b>	<b>Incisional</b>	<b>Space</b>	<b>Any</b>	<b>Incisional</b>	<b>Incisional</b>	<b>Space</b>	<b>Any</b>	<b>Any</b>
	<b>(12 cases)</b>	<b>(3 cases)</b>	<b>(8 cases)</b>	<b>(23 cases)</b>	<b>(19 cases)</b>	<b>(9 cases)</b>	<b>(9 cases)</b>	<b>(37 cases)</b>	<b>(60 cases)</b>
Gram-positive aerobic bacteria									
<i>Staphylococcus aureus</i> †	7	0	1	8	12	2	2	16	24
<i>Staphylococcus epidermidis</i> ‡	4	1	0	5	4	2	1	7	12
Enterococci	3	1	2	6	2	2	2	6	12
Streptococci	0	0	1	1	5	3	2	10	11
Corynebacteria‡	2	0	0	2	1	0	1	2	4
Gram-negative aerobic bacteria									
<i>Escherichia coli</i>	1	1	1	3	1	0	0	1	4
<i>Klebsiella pneumoniae</i>	1	0	1	2	1	1	0	2	4

Enterobacter species	0	0	2	2	0	0	2	2	4
Anaerobic bacteria									
Bacteroides species	3	2	2	7	1	2	2	5	12
Fungi									
Candida species	0	0	0	0	0	3	1	4	4

\* This table lists only organisms that were isolated from >5% of cases (3 cases) of infection with documented organisms. Less frequently isolated organisms included *Pseudomonas aeruginosa*, (3 cases), citrobacter species (2 cases), *Morganella morganii* (1 case), *Proteus mirabilis* (1 case), *Aeromonas hydrophila* (1 case), peptostreptococcus species (1 case), *Propionibacterium acne* (1 case), *Provetella melaninogenica* (1 case), and 5 unidentified Gram-negative aerobic bacilli. The total of 107 isolates included 44 strains from the chlorhexidine-alcohol group vs. 63 strains from the povidone-iodine group and comprised 63 Gram-positive aerobic bacterial isolates (22 vs. 41), 25 Gram-negative aerobic bacterial isolates (13 vs. 12), 15 anaerobic bacterial isolates (9 vs. 6), and 4 fungal isolates (0 vs. 4). The 14 excess cases of infection in the povidone-iodine group were primarily accounted for by *S. aureus* and streptococci which caused 22 cases of superficial and deep incisional infection in this group vs. 7 in the chlorhexidine-alcohol group. The 60 cases of infection with identified microbiology occurred after 53 abdominal, 5 thoracic, 1 gynecologic, and 1 urologic surgeries.

† Ten of the 24 strains of *S. aureus* were methicillin-resistant and were proportionately distributed between the two study group (3 in the chlorhexidine-alcohol group and 7 in the povidone-iodine group).

‡ All isolates of *S. epidermidis* and corynebacteria grew from polymicrobial cultures except in 1 case of infection each.

**Table 5 (full). Clinical Adverse Events (Intention-to-Treat Population).**

Clinical adverse event	Chlorhexidine-Alcohol	Povidone-Iodine	Absolute Difference*		
	(N=409)	(N=440)	%	(95% CI)	P-Value <sup>†</sup>
<b>Adverse events</b>					
<b>(≥5% of patients in either study group)</b>					
Patients with adverse events	228 (55.7)	256 (58.2)	-2.4	(-9.1 to 4.2)	0.49
Type of event					
Abnormal cardiac rhythm or rate	25 (6.1)	25 (5.7)	0.4	(-2.7 to 3.6)	0.88
Nausea	30 (7.3)	34 (7.7)	-0.4	(-3.9 to 3.2)	0.90
Urinary tract infection	23 (5.6)	28 (6.4)	-0.7	(-3.9 to 2.5)	0.67
Abdominal pain	21 (5.1)	29 (6.6)	-1.5	(-4.6 to 1.7)	0.39
Ileus	19 (4.6)	24 (5.5)	-0.8	(-3.8 to 2.1)	0.64

**Table 5 (full). Clinical Adverse Events (Intention-to-Treat Population).**

	Chlorhexidine-Alcohol	Povidone-Iodine	Absolute Difference*		
	(N=409)	(N=440)	%	(95% CI)	P-Value <sup>†</sup>
<b>Clinical adverse event</b>	<b>no. (%)</b>	<b>no. (%)</b>			
Patients with drug-related adverse events‡	3 (0.7)	3 (0.7)	0.1	(-1.1 to 1.2)	>0.99
<b>Serious adverse events</b>					
(≥1% of patients in either study group)					
Patients with serious adverse events	72 (17.6)	70 (15.9)	1.7	(-3.3 to 6.7)	0.52
Type of event					
Bloodstream infection	11 (2.7)	23 (5.2)	-2.5	(-5.1 to 0.1)	0.08
Abscess	6 (1.5)	11 (2.5)	-1.0	(-2.9 to 0.8)	0.33
Pneumonia	6 (1.5)	9 (2)	-0.6	(-2.3 to 1.2)	0.61

**Table 5 (full). Clinical Adverse Events (Intention-to-Treat Population).**

Clinical adverse event	Chlorhexidine-Alcohol	Povidone-Iodine	Absolute Difference*		
	(N=409) no. (%)	(N=440) no. (%)	%	(95% CI)	P-Value <sup>†</sup>
Bowel ischemia	7 (1.7)	8 (1.8)	-0.1	(-1.9 to 1.7)	>0.99
Anastomotic leak	9 (2.2)	4 (0.9)	1.3	(-0.4 to 3.0)	0.16
Acute renal failure	5 (1.2)	7 (1.6)	-0.4	(-1.9 to 1.2)	0.77
Respiratory failure	4 (1)	8 (1.8)	-0.8	(-2.4 to 0.7)	0.39
Bowel obstruction	3 (0.7)	5 (1.1)	-0.4	(-1.7 to 0.9)	0.73
Patients with serious drug-related adverse events	0	0	---	---	---
Death	4 (1)	3 (0.7)	0.3	(-0.9 to 1.5)	0.72

**Table 5 (full). Clinical Adverse Events (Intention-to-Treat Population).**

	Chlorhexidine-Alcohol	Povidone-Iodine	Absolute Difference*		
	(N=409)	(N=440)	%	(95% CI)	P-Value <sup>†</sup>
Clinical adverse event	no. (%)	no. (%)			

\* The absolute difference is shown as the rate in the chlorhexidine-alcohol group minus the rate in the povidone-iodine group.

<sup>†</sup> P-values were calculated with the use of Fisher's exact test.

<sup>‡</sup> Drug-related adverse events included pruritis, erythema, or both around the surgical wound. These events are reported even though the rate was not 5% or higher in either group.

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