

L'importanza del source control in infettivologia

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Genova

13th ACCP

Starhotel President

Genova, 17 Novembre 2023

15:45-16:00



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Disclosures

- Research grants

- Ethos SRL
- Università degli studi di Milano Bocconi.
- PKG
- MSD
- Pfizer
- Shionogi

NON SONO UN CHIRURGO!



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Che cosa si intende per source control?



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Cosa intendiamo per *source control*?

Storicamente...

**UBI PUS, IBI
EVACUA**

Galeno di Pergamo (Pergamo, 129 – Roma, 201 circa)



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Cosa intendiamo per *source control*?

1. Eliminare la fonte dell'infezione
2. Ripristinare l'anatomia e la funzione dell'organo
3. Controllare la contaminazione batterica



Oggi...

- 1) Drenaggio di raccolte ascessuali infette
- 2) *Toilette* chirurgica di tessuto solido infetto
- 3) Rimozione di *devices* e corpi estranei (inclusi CVC, stent, protesi etc.)
- 4) Correzione di alterazioni anatomiche che siano responsabili di infezioni recidivanti



Quanto è importante un adeguato controllo del focolaio infettivo?



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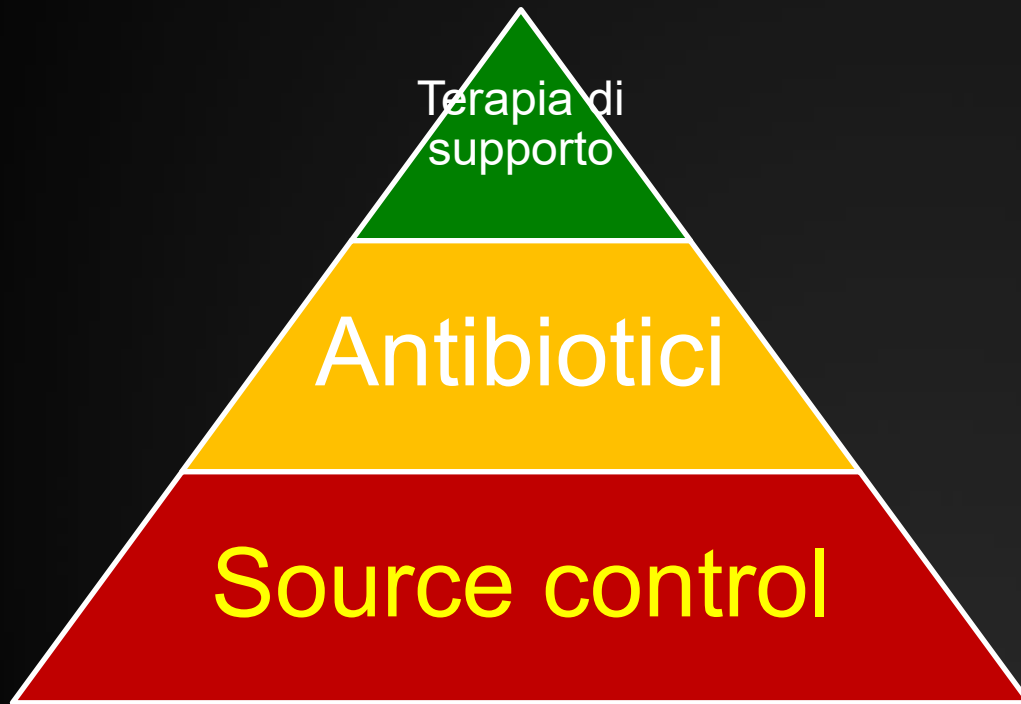


Poor timing and failure of source control are risk factors for mortality in critically ill patients with secondary peritonitis

- Analisi post hoc studio multicentrico osservazionale (AbSeS)
- 1077 pz in TI con peritonite microbiologicamente confermata
- Mortalità totale **29%**
- Fattori di rischio associati a mortalità (analisi multivariata):
 - **Shock settico** (OR 3.08, 95% CI, 1.42–7.00)
 - Tp empirica appropriata (OR 0.78, 95% CI, 0.55–1.09 → NS).
 - **Peritonite ospedaliera** (OR 1.71; 1.16–2.52)
 - **Source control urgente (2-6 h)** (OR 0.50; 0.34–0.73)

il **source control** è, rispetto al trattamento empirico adeguato, la variabile determinante per l'evoluzione clinica del paziente.

Gestione del paziente infetto in assenza di source control



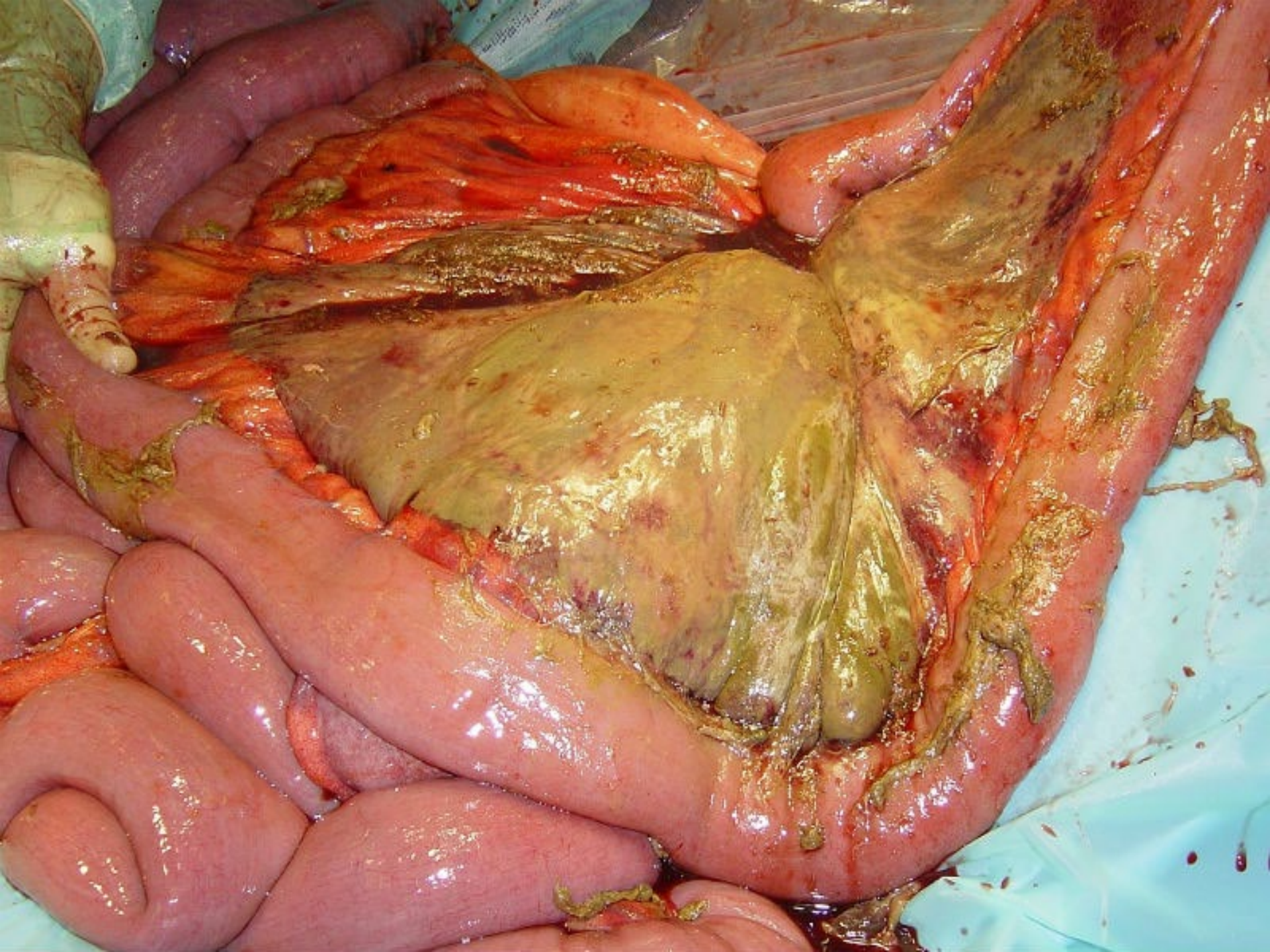
Chi dovrebbe essere sottoposto ad un adeguato controllo del focolaio infettivo?



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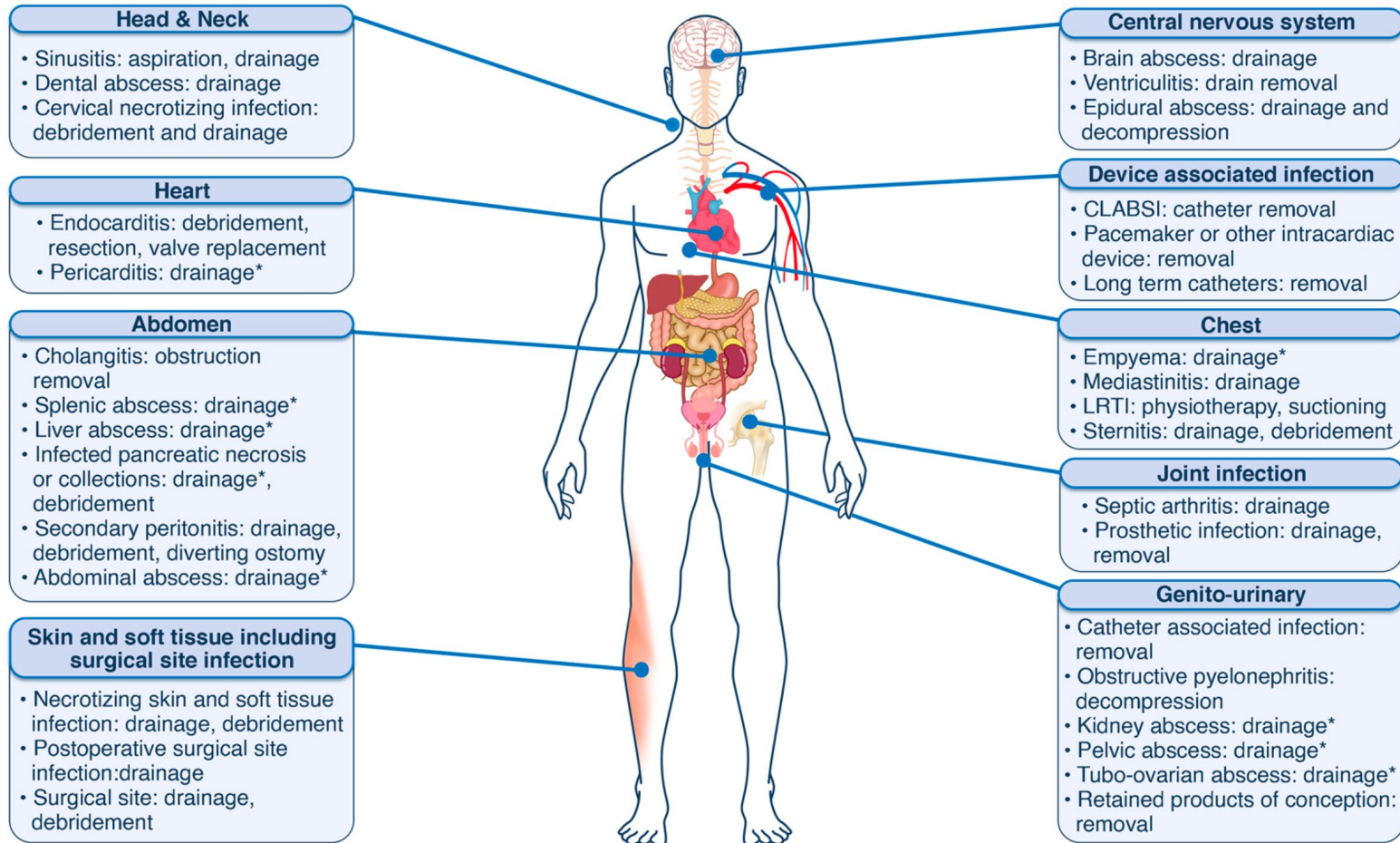




Source control

Indicatore di qualità?

De Waele JJ, et al. Intensive Care Med. 2022.



5 STEPS TOWARDS A SUCCESSFULL PERSONALIZED APPROACH FOR SOURCE CONTROL IN SEPSIS AND SEPTIC SHOCK:

1. Maximal effort for diagnosis
2. Multidisciplinary management
3. Promptly but not aggressive
4. Resolutely but not excessive
5. Continuous reassessment



Perché è importante il *source control*?



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Perché è necessario il *source control*?

- 1) Miglioramento dell'*outcome* clinico e riduzione della mortalità



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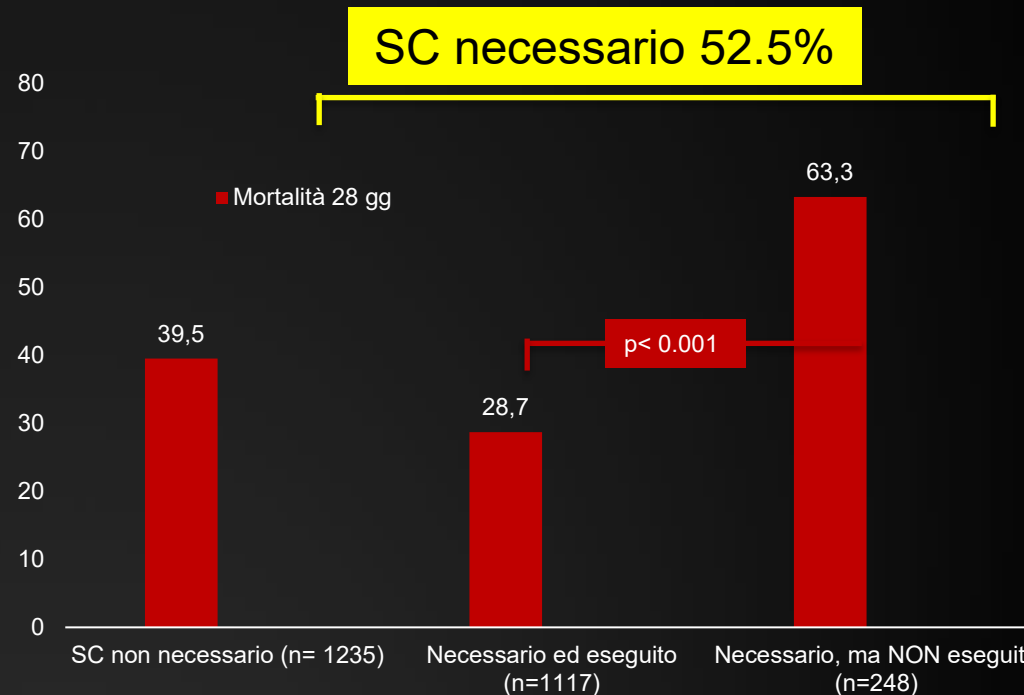
Ruolo del *source control* nella peritonite secondaria

Autore	Rivista	anno	n	Mortalità con adeguato source control	Mortalità SENZA source control
Bartels	Chirurg	1992	184	9,3%	100%
Billing	Br J Surg	1992	377	14%	64%
Büchler	Chirurg	1997	186	14%	40%
Koperna	World J Surg	2000	105	40%	100%
Seiler	Surgery	2000	258	14%	59%



Studio Eurobact

- **Studio di coorte prospettico**
- Adulti con BSI nosocomiali gestiti in TI
- 2600 pazienti; origine più frequente polmonite (26.7%)>>CVC (26.4%)
- Bacilli gram-negativi (59.0%)
- Tp antibiotica adeguata (<24h): 51.5%
- Mortalità 28 gg: 37.1%



Tabah A, Intensive care medicine 2023



Non solo addome..



Presentation and outcomes of necrotizing soft tissue infections

Table 2 Summary of demographics, presentation, and outcomes for the 60 cases of NSTI studied

Variable	Study result
Patient demographics	
Mean age, years (SD)	53.7 (17.8)
Sex, male	60%
Immune compromise	58%
Vascular disease	45%
Diabetes mellitus	42%
Obesity	25%
Initial presentation	
Swelling	92%
Erythema	87%
Bruising	45%
Bullae	28%
Petechiae	8%
Location	
Upper extremity	17%
Lower extremity	55%
Trunk	23%
Multiple sites	5%
Outcomes	
Median (IQR) length of hospital stay	17.1 days (7.8, 33.5)
In-hospital mortality with surgery	14%
In-hospital mortality without surgery	60%

Abbreviations: IQR, interquartile range; NSTI, necrotizing soft tissue infection.

- 60 pazienti con infezione necrotizzante di cute e tessuti molli
- 83% source control chirurgico

Chen KC, Int J Gen Med 2017

5 volte superiore

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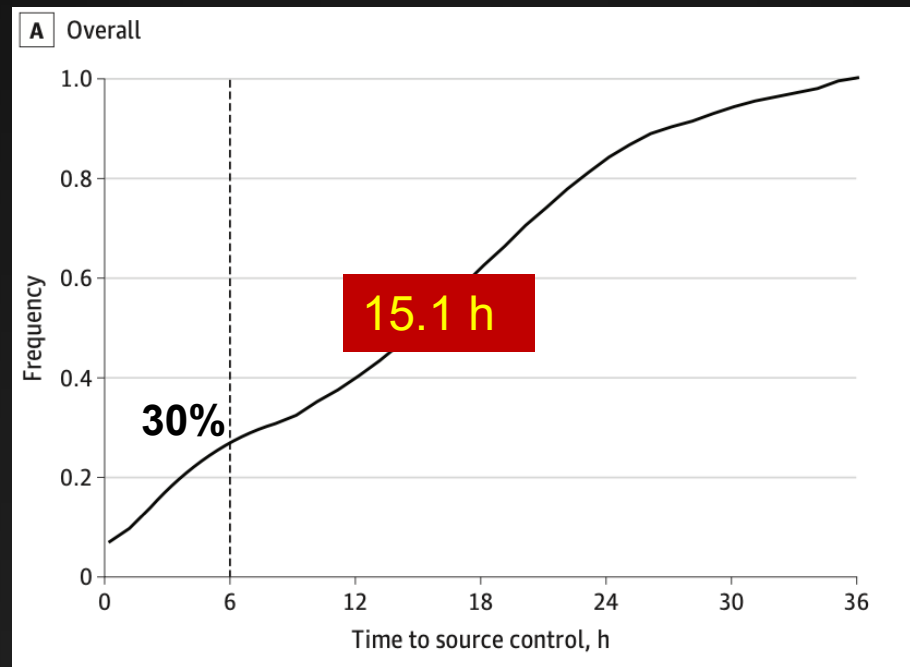


Tempistiche adeguate in termine di adeguato controllo del focolaio infettivo

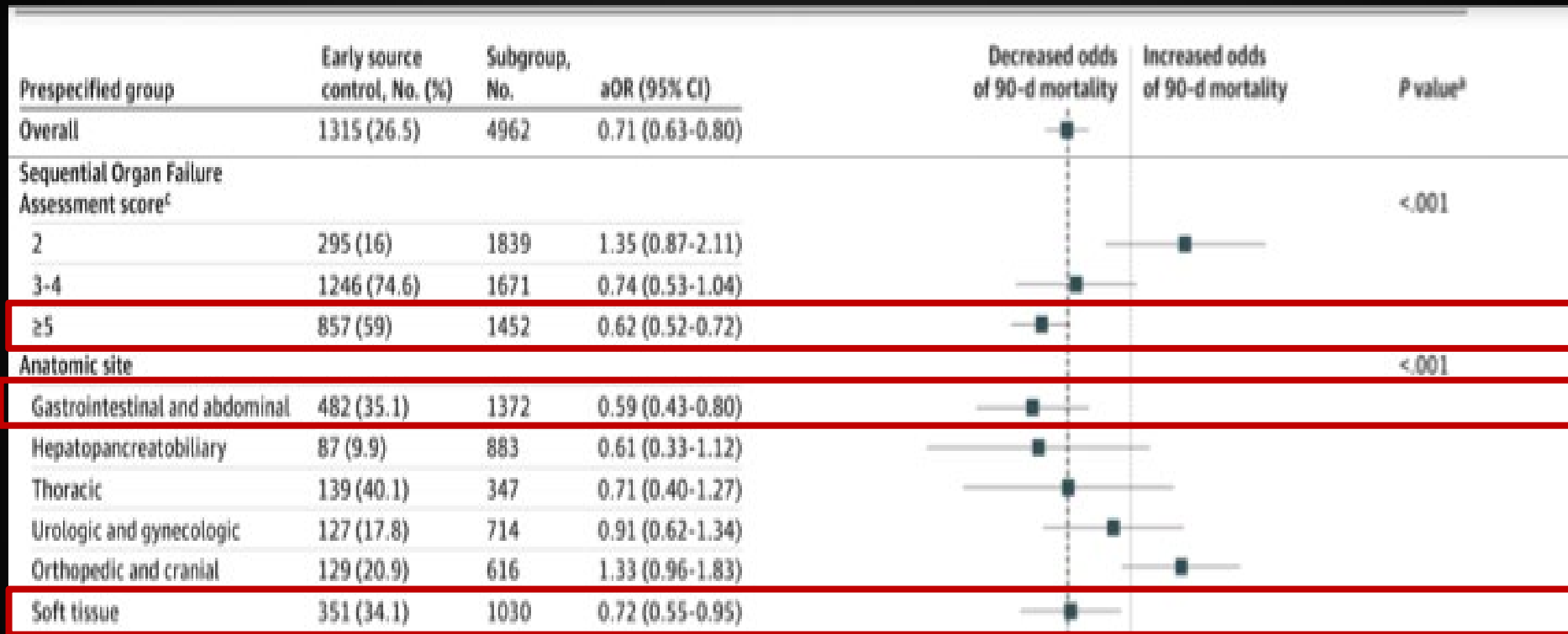


Association Between Time to Source Control in Sepsis and 90-Day Mortality

- Studio retrospettivo con 4962 pz con sepsi comunitaria che richiedeva un SC.
- Confronto tra il controllo precoce (<6 h) e quello tardivo (6-36 ore) della fonte, così come ogni ora di ritardo nel controllo della fonte (1-36 ore) dall'inizio della sepsi.

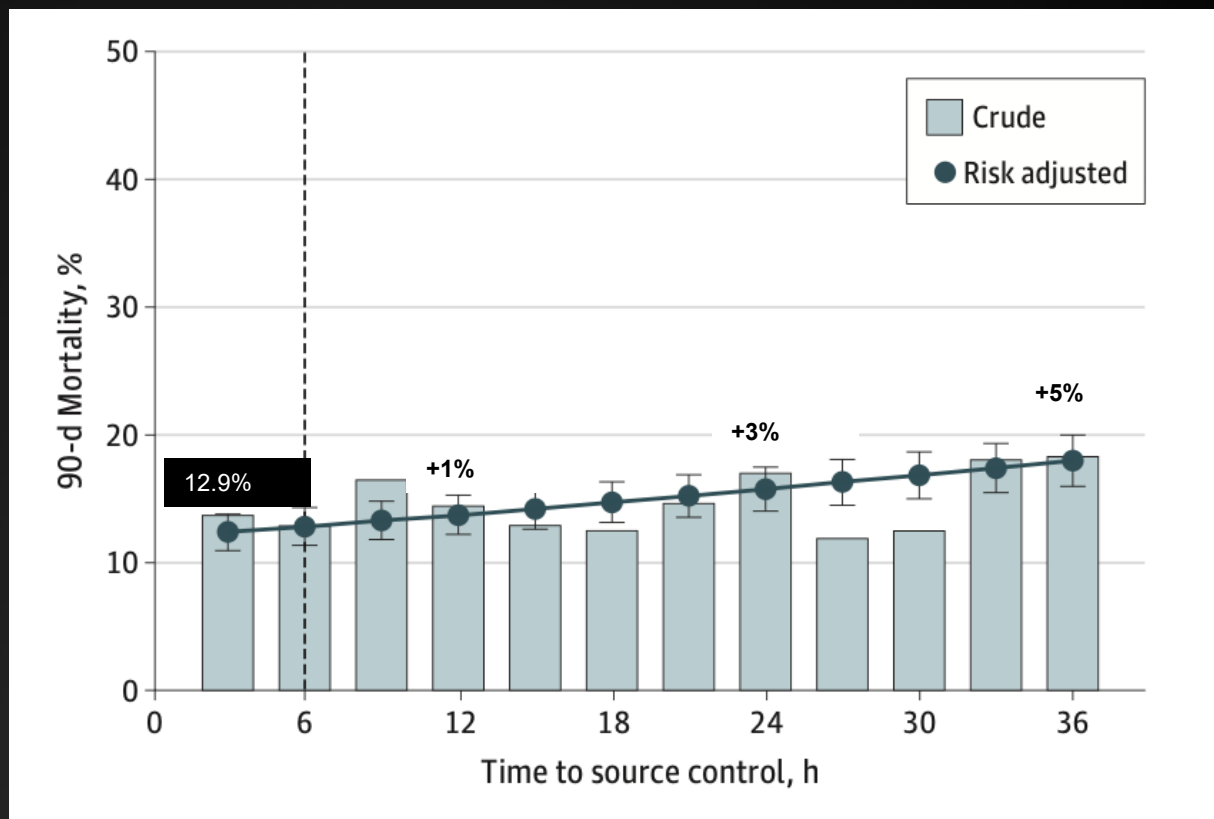


Association Between Time to Source Control in Sepsis and 90-Day Mortality



Association Between Time to Source Control in Sepsis and 90-Day Mortality

Ogni ora di ritardo nel SC si associava ad un aumento della mortalità a 90 gg (aOR 1.02)



Katherine M. Reitz, JAMA surg 2022



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Perché è necessario il *source control*?

- 1) Miglioramento dell'*outcome* clinico e riduzione della mortalità
- 2) **Penetrazione inadeguata degli antibiotici nelle raccolte ascessuali e nei tessuti necrotici (ampia variabilità, scarsamente predicibile)**



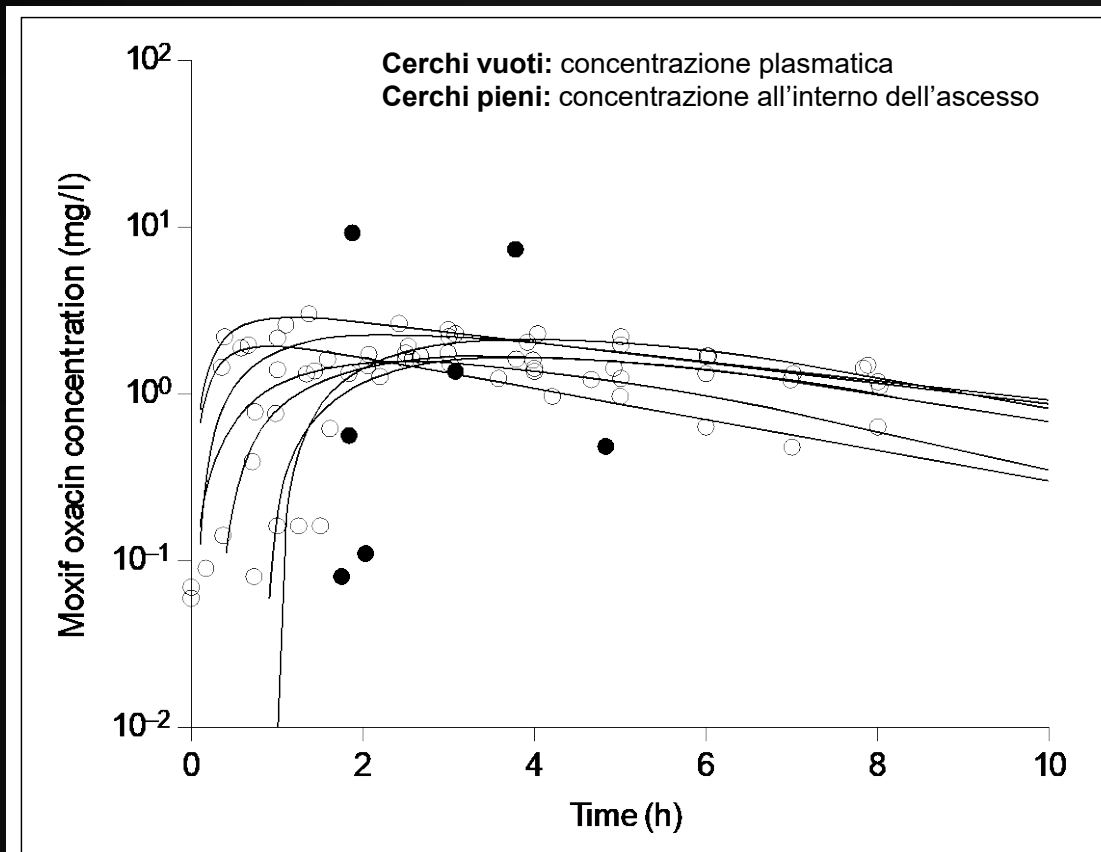
Good Penetration of Moxifloxacin into Human Abscesses

10 accessi

Valutazione della [] di moxifloxacina (400 mg ev) plasmatica e all'interno dell'ascesso

Risultati:

- 3/10 casi: non dosabile
- ampia variabilità



Sauermann R et al, Pharmacology. 2012 4



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- 3) Problema dell'efficacia degli antibiotici nei confronti del biofilm (devices e corpi estranei)**

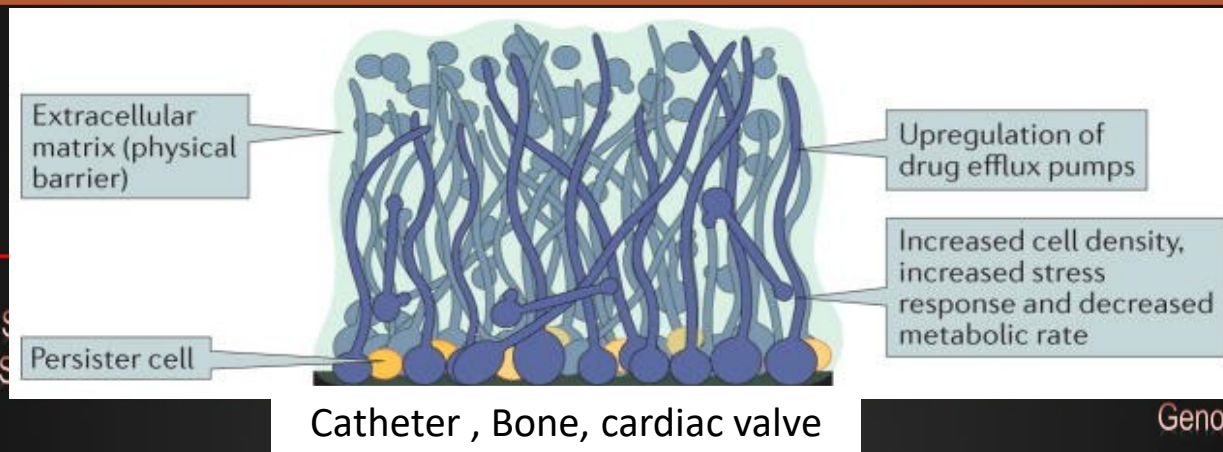


Che cosa è il biofilm?

Lohse MB et al; Nat Rev Microbiol 2018

Importanza clinica

1. Una volta che il biofilm si è formato, le infezioni associate ai device diventano più difficili da trattare
2. La formazione del biofilm può portare ad un alterato funzionamento del device stesso.



Risk Factors and Outcomes of Candidemia Caused by Biofilm-Forming Isolates in a Tertiary Care Hospital

Mario Tumbarello^{1*}, Barbara Fiori², Enrico Maria Trecarichi¹, Patrizia Posteraro³, Angela Raffaella Losito¹, Alessio De Luca⁴, Maurizio Sanguinetti², Giovanni Fadda², Roberto Cauda¹, Brunella Posteraro⁵

Hospital mortality, post-CBSI hospital length of stay (LOS) (calculated only among survivors), and costs of antifungal therapy were significantly greater among patients infected by biofilm-forming isolates than those infected by non-biofilm-forming isolates. Among biofilm-forming CBSI patients receiving adequate antifungal therapy, those treated with highly active anti-biofilm (HAAB) agents (e.g., caspofungin) had significantly shorter post-CBSI hospital LOS than those treated with non-HAAB antifungal agents (e.g., fluconazole); this difference was confirmed when this analysis was conducted only among survivors.

ORIGINAL ARTICLE

MYCOLOGY

Biofilm formation is a risk factor for mortality in patients with *Candida albicans* bloodstream infection—Scotland, 2012–2013

R. Rajendran¹, L. Sherry¹, C. J. Nile¹, A. Sherriff¹, E. M. Johnson², M. F. Hanson³, C. Williams⁴, C. A. Munro⁵, B. J. Jones⁶ and G. Ramage¹

Available

mortality data for 134 patients showed that the 30-day candidaemia case mortality rate was 41%, with predisposing factors including patient age and catheter removal. Multivariate Cox regression survival analysis for 42 patients showed a significantly higher mortality rate for *Candida albicans* infection than for *Candida glabrata* infection. Biofilm-forming ability was significantly associated with *C. albicans* mortality (34 patients). Finally, *in vitro* antifungal sensitivity testing showed that low biofilm formers and high biofilm formers were differentially affected by azoles and echinocandins, but not by polyenes. This study provides further evidence that the biofilm phenotype represents a significant clinical entity, and that isolates with this phenotype differentially respond to antifungal therapy *in vitro*. Collectively, these findings show that greater clinical



Is biofilm production a prognostic marker in adults with candidaemia?

P. Muñoz^{1,2,3,4,†}, C. Agnelli^{1,2,*†}, J. Guinea^{1,2,3,4}, A. Vena^{1,2}, A. Álvarez-Uría^{1,2},
L.J. Marcos-Zambrano^{1,2}, P. Escribano^{1,2}, M. Valerio^{1,2}, E. Bouza^{1,2,3,4}

- **Obiettivo:** Analizzare l'impatto della formazione del biofilm
 - **Mortalità a 7 e 30 gg.**
 - **Complicanze metastatiche** (candidiasi oculare, Tromboflebite, EI)
 - **Ricovero in TI**

Muñoz P et al; Clin Microb Infect 2018



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Evoluzione clinica dei pazienti con candidemia in funzione del livello di produzione di biofilm.

Variables	Total (<i>n</i> = 280)	Biomass		
		Moderate-Low ^a (<i>n</i> = 190)	High ^b (<i>n</i> = 90)	p-value
Metastatic complications ^e , <i>n</i> (%)				
Ocular metastasis	25/188 (13.3)	18/126 (14.3)	7/62 (11.3)	0.653
Thrombophlebitis	18/37 (48.6)	11/21 (52.4)	7/16 (43.8)	0.743
Endocarditis	3/214 (1.4)	3/146 (2.1)	0/68 (0.0)	0.553
Dissemination to other organs	12 (4.3)	5 (2.6)	7 (7.8)	0.060
Outcomes, <i>n</i> (%)				NS
ICU admission	28 (10.0)	22 (11.6)	6 (6.7)	0.180
7-day mortality	39 (13.9)	24 (12.6)	15 (16.7)	0.362
30-day mortality	95 (33.9)	61 (32.1)	34 (37.8)	0.418
Unfavourable prognosis ^f	118 (38.2)	73 (38.4)	45 (50.0)	0.071
Microbiological eradication ^g	201/219 (91.8)	135/151 (89.4)	66/68 (97.1)	0.065
LOHS, median in days (range) ^h	19 (0-254)	25 (3-254)	21 (5-143)	0.547

Is biofilm production a prognostic marker in adults with candidaemia?

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Supplementary Table S2. Factors associated with the prognosis of candidemia according to the univariate analysis.

method and species. Also, it was performed in a single centre, with a structured antifungal stewardship programme that ensured a high percentage of appropriate source control, which could have minimized the clinical impact of biofilm production. However,

<i>Candida parapsilosis</i>	47 (29.0)	17 (14.4)	0.006
<i>Candida tropicalis</i>	12 (7.4)	15 (12.7)	0.154
Echinocandin as initial treatment	48 (29.6)	37 (31.4)	0.793
Adequate antifungal treatment	157 (96.9)	98 (83.1)	<0.001
Time to adequate antifungal – median in days (range)	2 (0-11)	2 (0-9)	0.249
Adequate antifungal within 48 hours	109 (69.0)	75 (72.8)	0.579
Infection source control	122/129 (94.6)	64/86 (74.4)	<0.001

* Unfavorable prognosis was defined as any patient with at least one of the following: metastatic complication, admission to an intensive care unit due to the severity of the candidemia episode, or death within 30 days

adequate
source
control!!!



Perché è necessario il *source control*?

- 1) Miglioramento dell'*outcome* clinico e riduzione della mortalità
- 2) Penetrazione inadeguata degli antibiotici nelle raccolte ascessuali e nei tessuti necrotici (ampia variabilità, scarsamente predicibile)
- 3) Problema dell'efficacia degli antibiotici nei confronti del biofilm (devices e corpi estranei)
- 4) **Diagnosi microbiologica e resistenze antibiotiche**



Source control e diagnosi microbiologica

3,663 pazienti con sepsi grave o SS; 1,173 (32%) che richiedevano SC

Patient Characteristic	All Patients, <i>n</i> = 3,663	Patients Not Requiring Source Control, <i>n</i> = 2,490 (68%)	Patients Requiring Source Control, <i>n</i> = 1,173 (32%)	<i>p</i>
General data				
Age (yr), mean (SD)	64 (15.1)	62.8 (15.2)	66.7 (14.6)	< 0.001
Sex (male), <i>n</i> (%)	2,319 (63.3)	1,621 (65.1)	698 (59.5)	0.001
Acute Physiology and Chronic Health Evaluation II, mean (SD)	21.8 (8.01)	22.03 (8.2)	21.3 (7.6)	0.010
Shock, <i>n</i> (%)	2,497 (68.2)	1,630 (65.5)	867 (73.9)	< 0.001
Charlson comorbidity score, mean (SD)	2.6 (2.3)	2.6 (2.3)	2.7 (2.2)	0.531
C-reactive protein (mg/dL), mean (SD) ^a	24.2 (13.7)	23.6 (13.9)	25.5 (12.9)	< 0.001
Procalcitonin (ng/mL), mean (SD) ^b	26.2 (37.6)	24.1 (34.7)	31.2 (43)	0.001
Bacteremia, <i>n</i> (%)	1,211 (40.1)	821 (37.9)	390 (45.5)	< 0.001
Appropriate antibiotic therapy, <i>n</i> (%)	1,911 (51.9)	1,231 (49.4)	670 (57.1)	< 0.001



Il problema delle resistenze

Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*²⁵

Other priority bacteria

Priority 1: critical

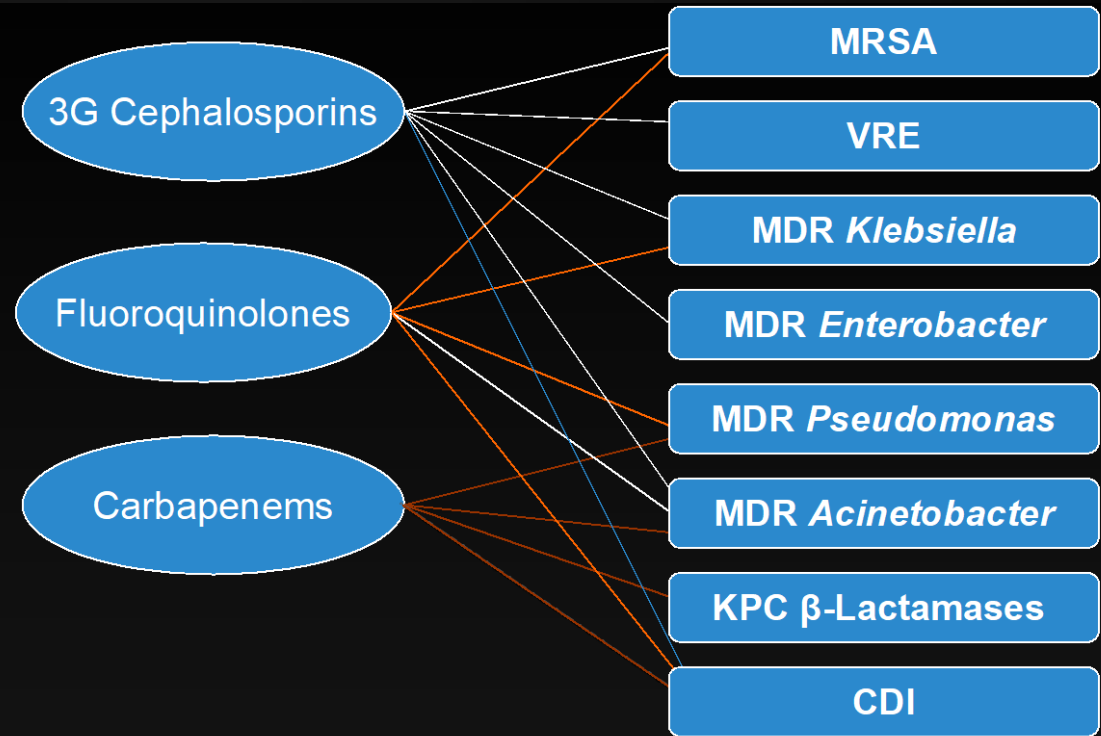
- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant



Lancet Infect Dis 2018; 18:318-327



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- 3) Problema dell'efficacia degli antibiotici nei confronti del biofilm (devices e corpi estranei)
- 4) Diagnosi microbiologica e resistenze antibiotiche
- 5) Ridurre la durata della terapia antibiotica**



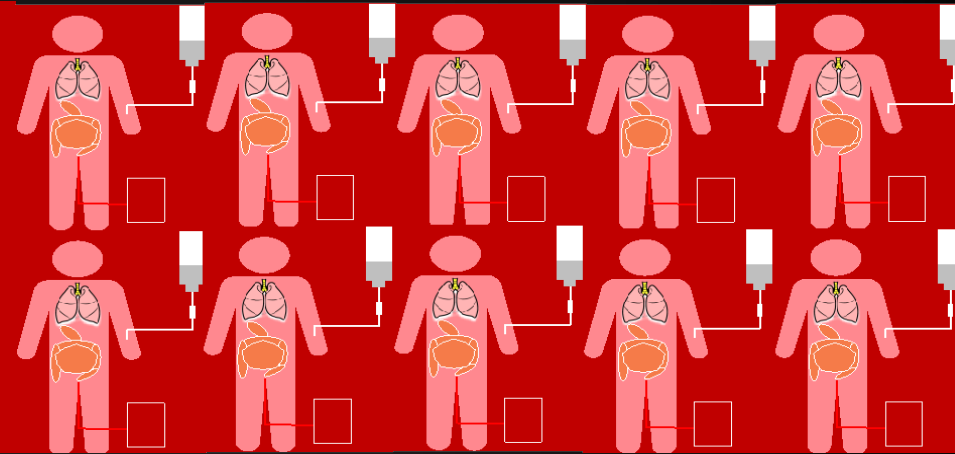
Stop it trial

clAI con adeguato source control

Gruppo di controllo

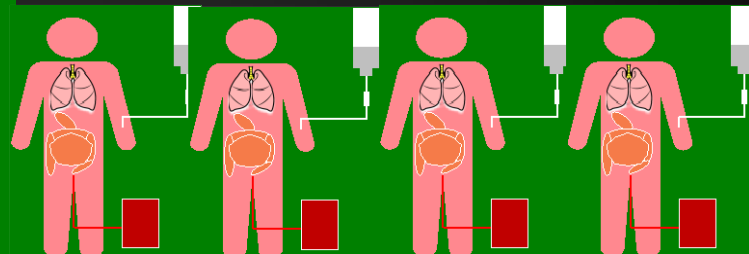
2 giorni oltre la risoluzione dei sintomi
(febbre, leucocitosi, e ileo)

MASSIMO 10 giorni di terapia



Gruppo sperimentale

4 giorni



Stop it trial

cIAI con adeguato SC

Gruppo di controllo

2 giorni oltre la risoluzione dei sintomi

MASSIMO 10 giorni di terapia

Gruppo sperimentale

4 giorni

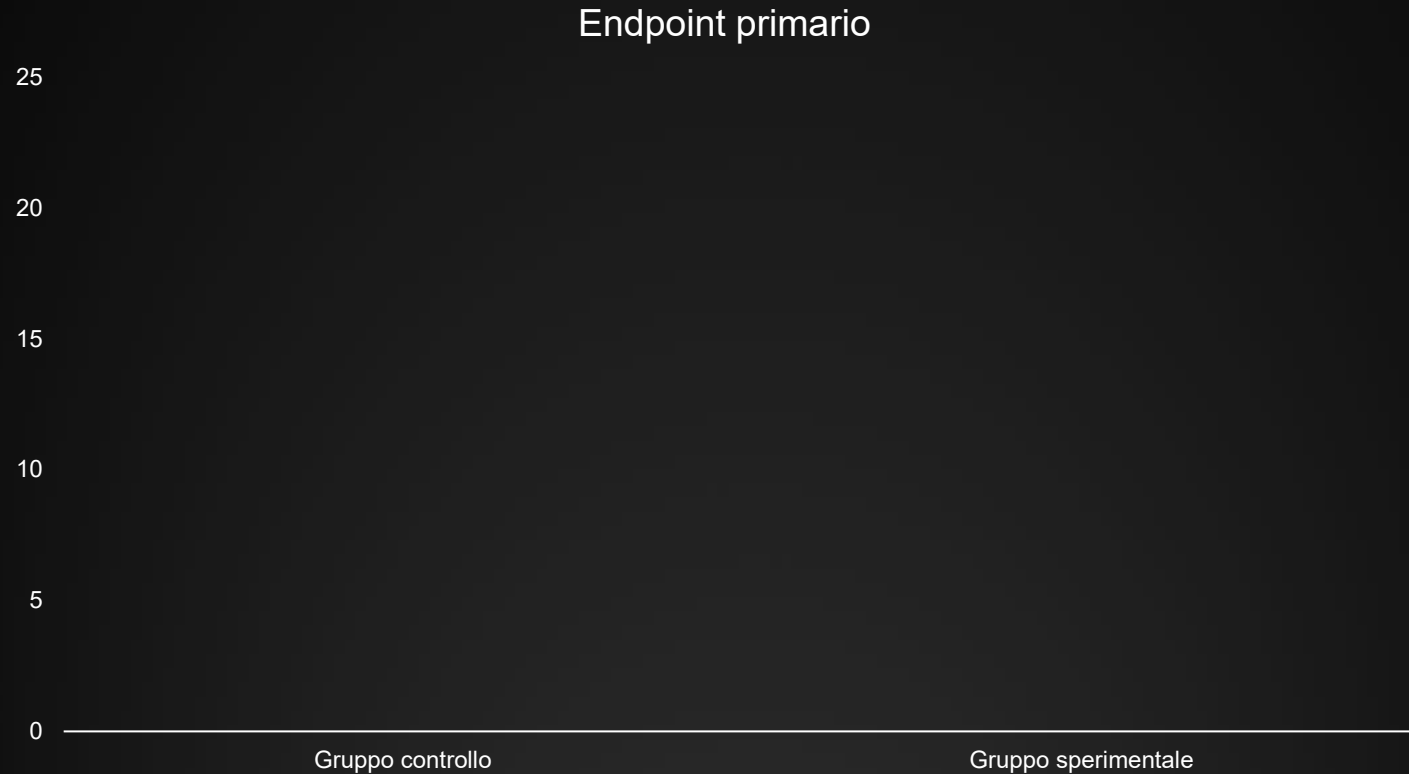
Endpoint primario

1. Infezione del sito chirurgico
2. IAI ricorrente
3. Morte (<30gg)



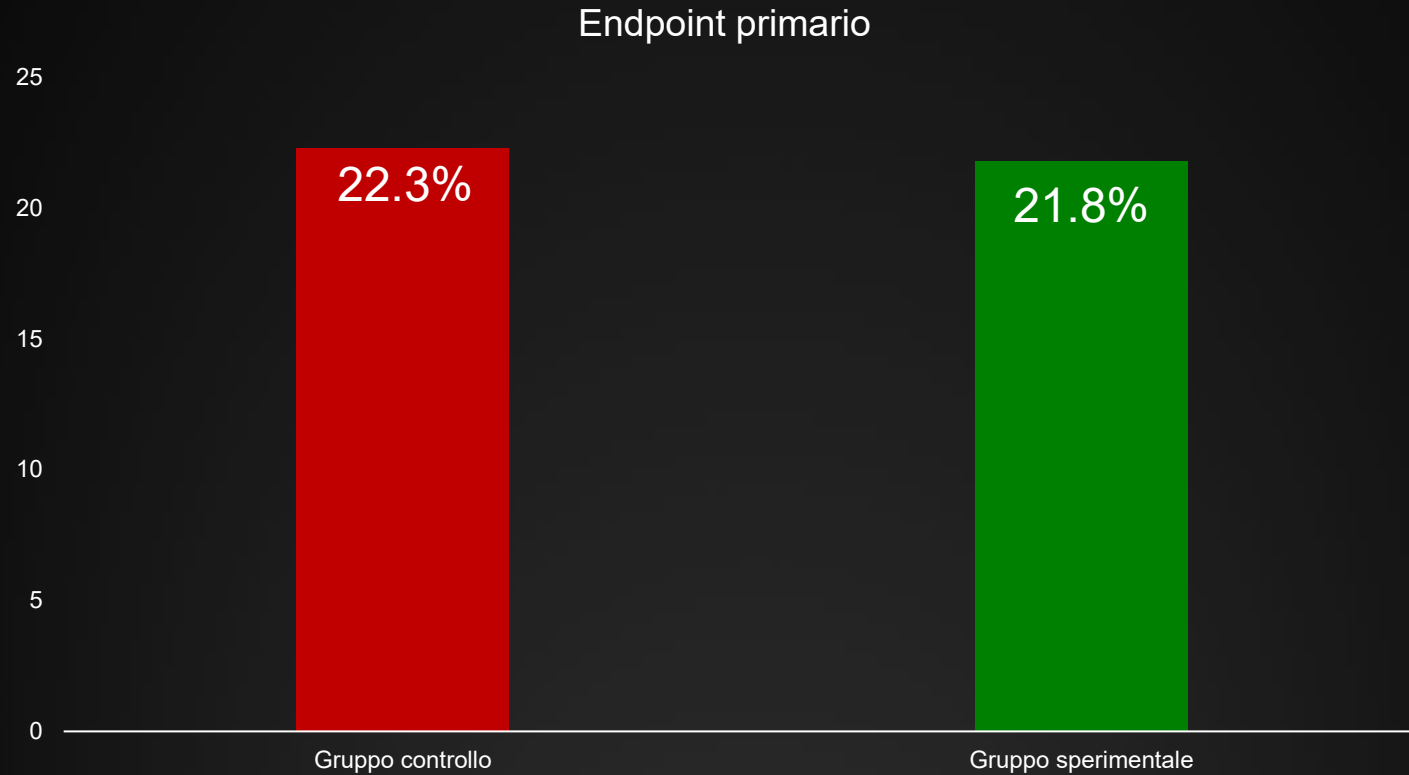
Stop it trial

clAI con adeguato SC



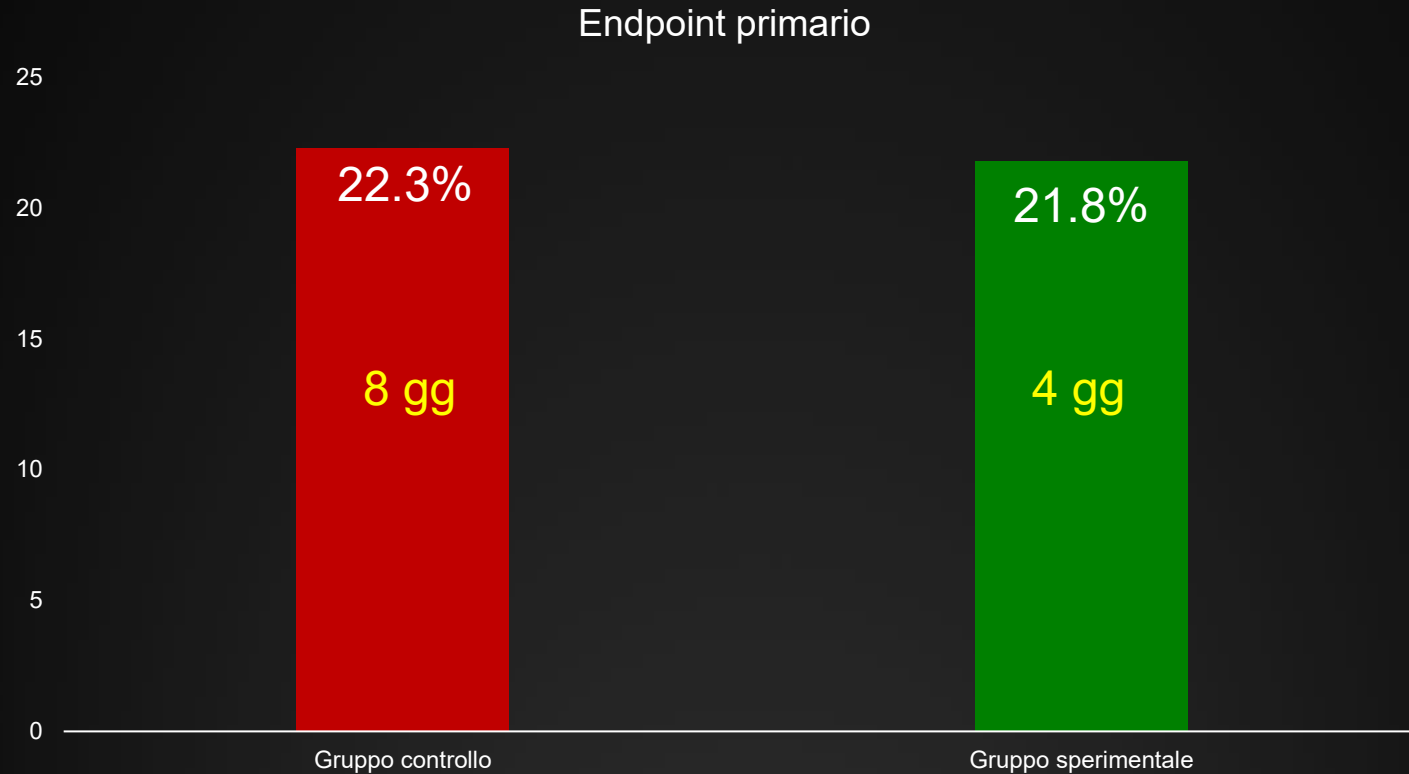
Stop it trial

clAI con adeguato SC



Stop it trial

clAI con adeguato SC



Non arrendersi mai



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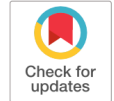
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Source control

van de Groep; J Crit care 2019

Epidemiology and outcomes of source control procedures in critically ill patients with intra-abdominal infection



Kirsten van de Groep^{a,b,*}, Tessa L. Verhoeff^c, Diana M. Verboom^{a,b}, Lieuwe D. Bos^d, Marcus J. Schultz^d, Marc J.M. Bonten^{a,e}, Olaf L. Cremer^b, on behalf of the MARS consortium

^a Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands

^b Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, the Netherlands

^c Department of Anesthesiology, University Medical Center Utrecht, Utrecht University, the Netherlands

^d Department of Intensive Care, Amsterdam University Medical Centers, University of Amsterdam, the Netherlands

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ABSTRACT

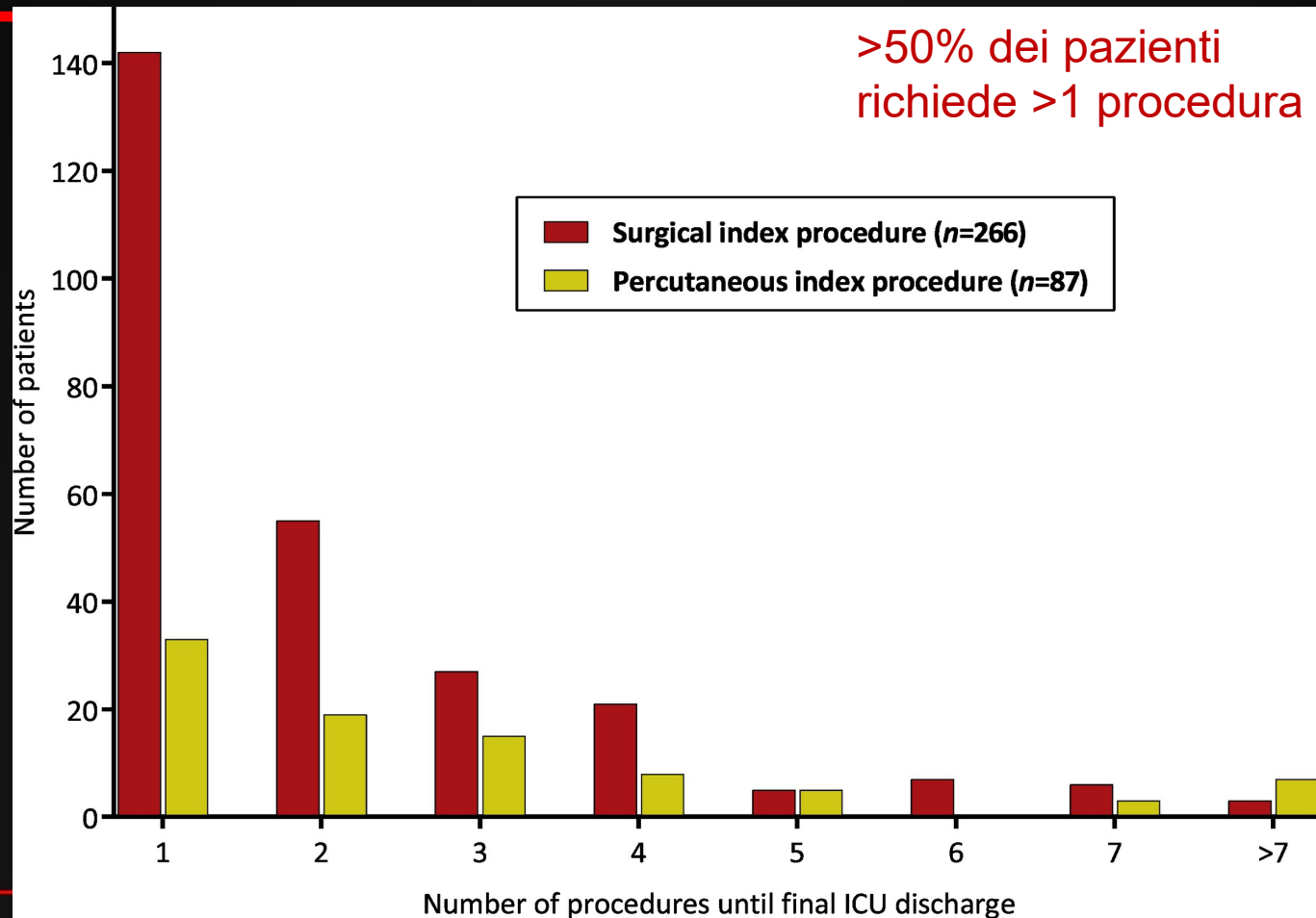
Purpose: To describe the characteristics and procedural outcomes of source control interventions among Intensive Care Unit (ICU) patients with severe intra-abdominal-infection (IAI).

Material and methods: We identified consecutive patients with suspected IAI in whom a source control intervention had been performed in two tertiary ICUs in the Netherlands, and performed retrospective in-depth case reviews to evaluate procedure type, diagnostic yield, and adequacy of source control after 14 days.

Results: A total of 785 procedures were observed among 353 patients, with initial interventions involving 266 (75%) surgical versus 87 (25%) percutaneous approaches. Surgical index procedures typically involved IAI of (presumed) gastrointestinal origin (72%), whereas percutaneous index procedures were mostly performed for infections of the biliary tract/pancreas (50%) or peritoneal cavity (33%). Overall, 178 (50%) patients required multiple interventions (median 3 (IQR 2–4)). In a subgroup of 236 patients having their first procedure upon ICU admission, effective source control was ultimately achieved for 159 (67%) subjects. Persistence of organ failure was associated with inadequacy of source control at day 14, whereas trends in inflammatory markers were non-predictive.

Conclusions: Approximately half of ICU patients with IAI require more than one intervention, yet successful source control is eventually achieved in a majority of cases.

Source control



Idea iniziale del chirurgo...

Variable	Source control by day 14						
	Adequate		Delayed adequate		Inadequate ^a		<i>p</i> -value
	<i>n</i> = 93 (39%)	<i>n</i> = 65 (28%)	<i>n</i> = 65 (28%)	<i>n</i> = 65 (28%)	<i>n</i> = 78 (33%)	<i>n</i> = 78 (33%)	
Immediate procedural adequacy	93	(100)	60	(92)	75	(96)	0.14
Adequacy on final assessment ^b	91	(98)	55	(85)	13	[17]	<0.001
Prior cultures available for guidance	13	[14]	6	[9]	8	[10]	0.60
Antimicrobial use on day 1:							
Beta-lactam ^c	93	(100)	64	(98)	73	(94)	0.02
Metronidazole	76	(82)	54	(83)	72	(92)	0.12
Vancomycin	12	[13]	1	[11]	12	[15]	0.77
Aminoglycoside	15	[16]	1	[24]	18	[23]	0.01
Antifungal	8	[9]	7	[11]	15	[19]	0.10
Other	8	[9]	2	[3]	4	[5]	0.37

Antimicrobial use from restricted formulary in first week:



Conclusione

- Source control è fondamentale affinché l'antibiotico possa funzionare
- L'adeguato source control non è un problema della sola cavità addominale.
- Applica precocemente (<6 h) un adeguato source control alla maggior parte dei pazienti (meno invasività se possibile)
- Fallimento del source control è un fenomeno intrinseco del paziente critico che richiede il source control (NON dipende dal chirurgo!).
- Pronti a re-intervenire!

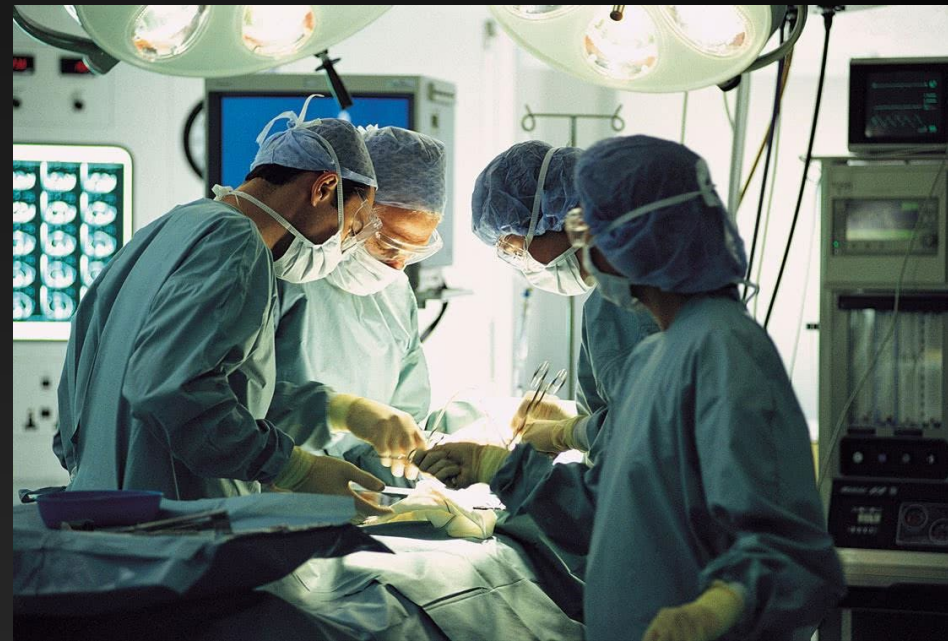


La mia speranza per il futuro

Bad Bugs
Need Drugs

10x'20

Ten new ANTIBIOTICS by 2020



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