Società Medico Chirurgica di Ferrara
"Antibioticoresistenza dei batteri: un problema da risolvere"
Cona 5 Novembre 2016

"La gestione nel setting chirurgico "

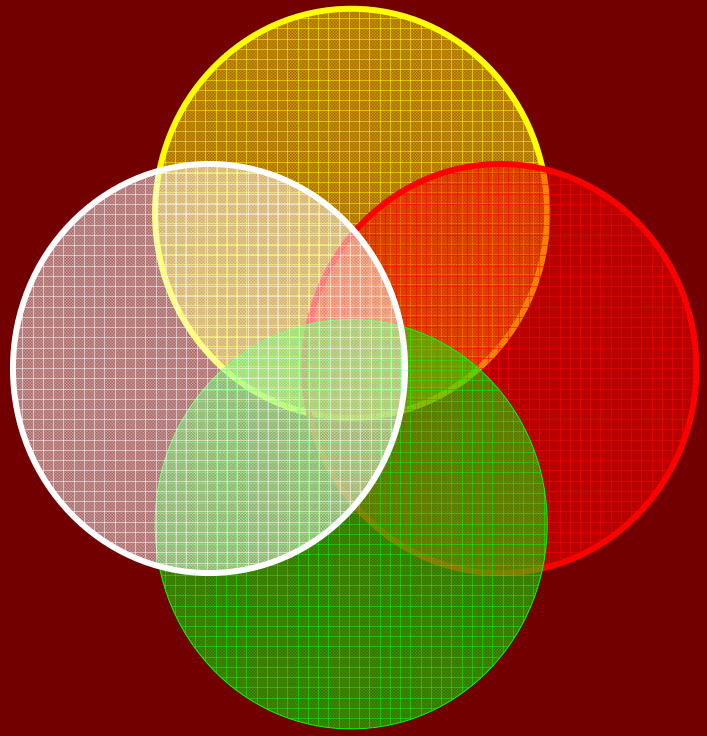
Marco Libanore

Unità Operativa Complessa
Malattie Infettive
Azienda Ospedaliera Universitaria Ferrara

Gestione della Sepsi Grave e dello Shock settico

Il paziente il fulcro del problema

Initial Resusitation



Source identification and control

Antimicrobic therapy

Diagnosis

Critical Care Med 41; 2: 2013

IAI : problematiche in gioco

- Forme comunitarie e associate alle cure sanitarie;
- Paziente critico o stabile ;
- **Impatto epidemiologico degli enterobatteri ESBL positivi ? ;**
- Localizzazione intestinale o biliare dell' infezione;
- **Quando considerare enterococco, pseudomonas e candida ?**
- **Possibilità d' infezioni/colonizzazioni da KPC ?;**
- Durata ottimale della terapia antimicrobica ;
- Regimi terapeutici alternativi senza carbapenemico;

Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study

Sartelli *et al. World Journal of Emergency Surgery* 2012, **7**:36
http://www.wjes.org/content/7/1/36

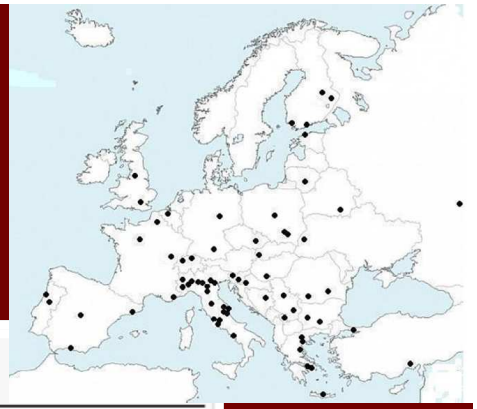
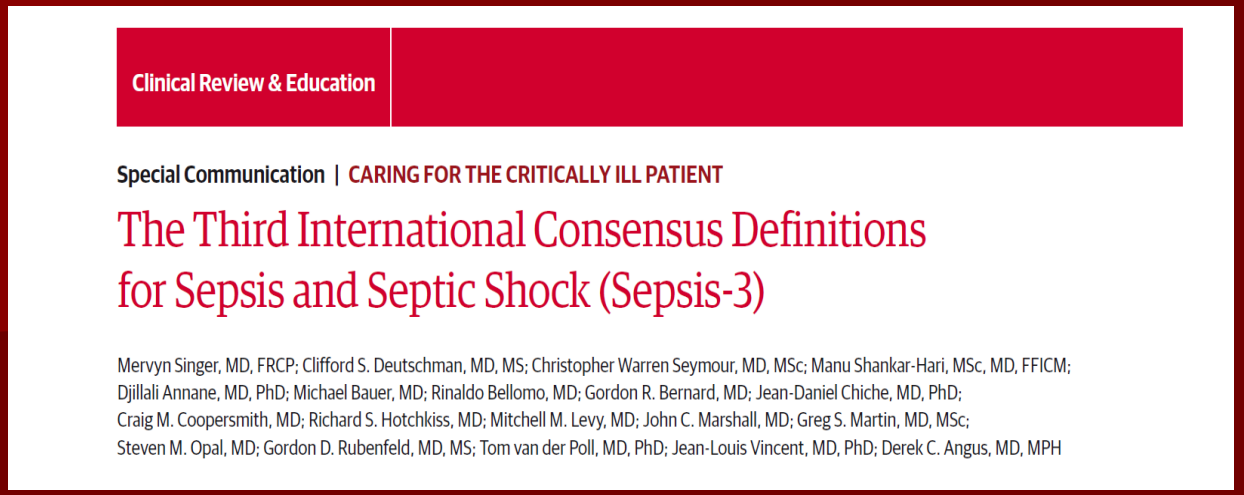


Table 3 Source of Infection

Source of infection	Patients N 2152° (100%)
Appendicitis	798 (37%)
Cholecystitis	289 (13.4%)
Post-operative	342 (15.,9%)
Colonic non diverticular perforation	158 (7.3%)
Gastroduodenal perforations	156 (7.3%)
Diverticulitis	166 (7.7%)
Small bowel perforation	103 (4.8%)
Others	110 (5.1%)
PID	18 (0.8%)
Post traumatic perforation	12 (0.6%)



Clinical Review & Education

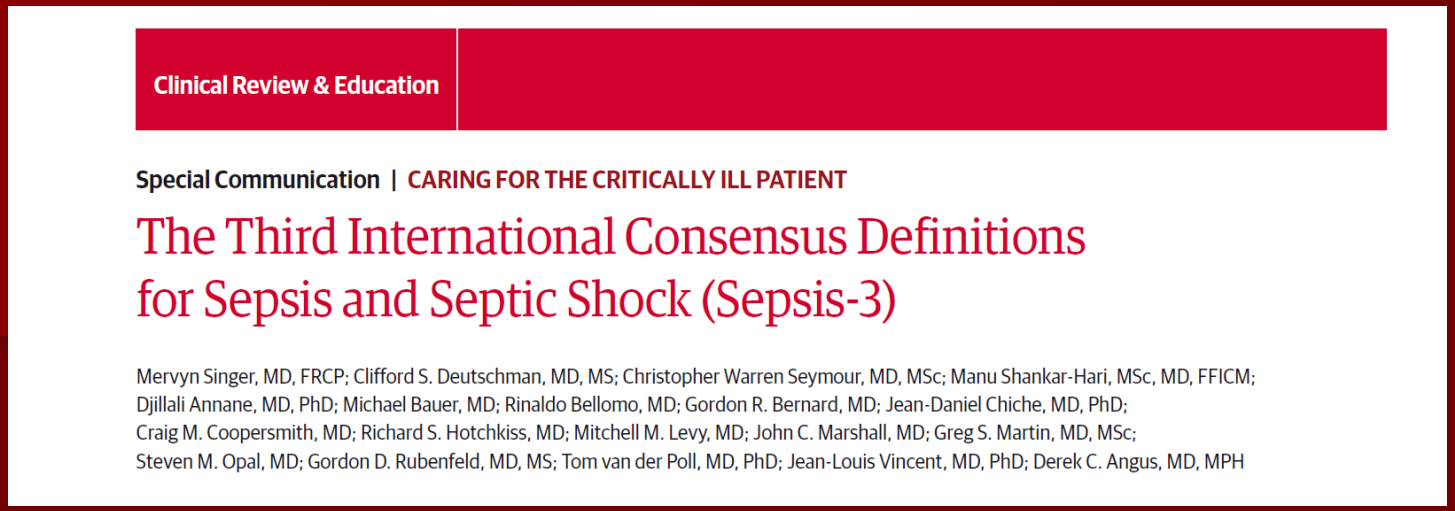
Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

SEPSI

Una disfunzione d'organo pericolosa per la vita, causata da una risposta disregolata dello ospite alle infezioni



SHOCK SETTICO

Una variabile della sepsi, in cui anomalie gravi a livello circolatorio, cellulare e metabolico sono associate a una maggiore mortalità, rispetto alla sepsi tradizionale;

Almeno 2 segni sotto indicati :

-Frequenza respiratoria > 22 atti/minuto

-Alterazione dello stato mentale

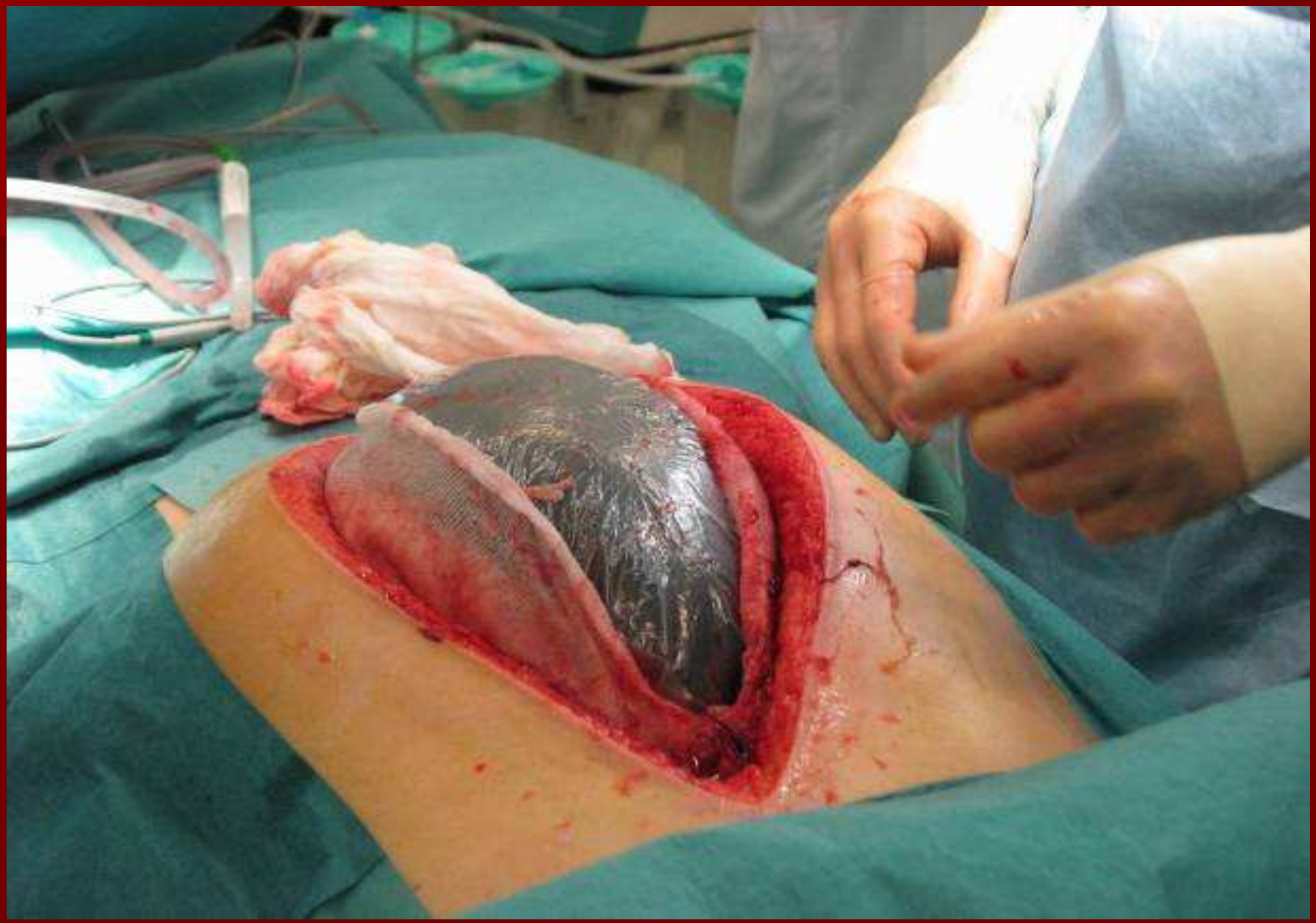
-Pressione arteriosa < 100 mmHg

STRATIFICAZIONE DEL RISCHIO: Score Sepsi

Sepsi (almeno 2 parametri + febbre o ipotermia)	T> 38,3°C < 36°C FC > 90 min. FR > 20 atti/min. Leucociti > 12.000/< 4.000/mmc Glicemia > 120 mg/dl Acido lattico > 2 mmol/L PCR > 2 SD oltre il valore normale Procalcitonina > 2 SD oltre il valore n Stato mentale alterato
Sepsi grave (sufficiente 1 parametro)	Ipotensione (PA sistolica < 90 mmHg) Lattacidemia > 4 mmol/L Disfunzione d' organo : renale (creatinina > 2 mg/dl ; oligoanuria), epatica (ALT > 2 v.n. o Bil.tot. > 2 mg/dl) , respiratoria (P/F < 250 o necessità di ventilazione meccanica) e coagulopatia (INR > 1,5 o piastrine < 100.000/mmc);
Shock settico	Ipotensione nonostante espansione volemica 20-40 ml/Kg in 1 ora

Gli steps della gestione clinica

- Trattare immediatamente la SIRS ;
- Rapida identificazione della sorgente infettiva ;
- Controllare e rimuovere prontamente il focus infettivo;
- Somministrare precocemente terapia antibiotica appropriata per eradicare l'infezione;



Hecker *et al. World Journal of Emergency Surgery* (2015) 10:54
DOI 10.1186/s13017-015-0047-0

WJES WORLD JOURNAL OF EMERGENCY SURGERY

RESEARCH ARTICLE Open Access

The impact of early surgical intervention in free intestinal perforation: a time-to-intervention pilot study

Andreas Hecker[1*†], E. Schneck[2†], R. Röhrig[2], F. Roller[3], B. Hecker[2], J. Holler[1], C. Koch[2], M. Hecker[4], M. Reichert[1], C. Lichtenstern[2], G. A. Krombach[3], W. Padberg[1] and M. A. Weigand[2]

Intervento chirurgico precoce vantaggioso nel paziente settico con patologia urgente

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i47.8799

World J Gastroenterol 2013 December 21; 19(47): 8799-8807
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Acute appendicitis: What is the gold standard of treatment?

Cesare Ruffolo, Alain Fiorot, Giulia Pagura, Michele Antoniutti, Marco Massani, Ezio Caratozzolo, Luca Bonariol, Francesco Calia di Pinto, Nicolò Bassi

CONCLUSION

Patient selection is important in both LA and OA. LA is the preferred approach in immunocompromised, obese and elderly patients. LA presents longer operative time, but also a shortening of hospital stay, a better and earlier recovery and return to everyday occupations and to work and, last but not least, a better cosmetic result.

Efficacia nel controllo del focus infettivo (Solomkin J CID 2013)

- Scomparsa della febbre ;
- Risoluzione della leucocitosi;
- Ripristino della normale funzione intestinale ;
- Nessuna necessità di reintervento chirurgico o percutaneo ;

Linee Guida : alcuni quesiti

- Forme comunitarie e associate alle cure sanitarie;
- Paziente critico o stabile ;
- Impatto epidemiologico degli enterobatteri ESLB positivi ;
- Quando considerare enterococco, psudomonas e candida ?
- Possibilità d' infezioni/colonizzazioni da KPC ? ;
- Localizzazione intestinale o biliare ;
- Regimi terapeutici alternativi al carbapenemico pur in presenza di MDR ;

Patogeni MDR in rapporto al tipo d'infezione

Table 2 Distribution of multiresistant bacteria by site of infection (patients with evaluable treatment outcome; $n = 215$)

Drug-resistance phenotype, % (n)	Patients with documented MRB infection			
	Any MRB	VRE	MRSA	ESBL
Total MRB population	100 % (215)	19.5 % (42)	61.4 % (132)	31.2 % (67)
Intraabdominal infection (cIAI)	32.6 % (70)	38.6 % (27)	27.1 % (19)	50.0 % (35)
Skin and soft tissue infection (cSSTI)	25.6 % (55)	5.5 % (3)	90.9 % (50)	7.3 % (4)
Diabetic foot infection (DFI)	14.0 % (30)	–(0)	100.0 % (30)	10.0 % (3)
Community-acquired pneumonia (CAP)	6.0 % (13)	7.7 % (1)	84.6 % (11)	38.5 % (5)
Hospital-acquired pneumonia (HAP)	14.0 % (30)	–(0)	70.0 % (21)	30.0 % (9)
Blood stream infection (BSI)	10.2 % (22)	18.2 % (4)	68.2 % (15)	36.4 % (8)
Multiple-site infection (MSI)	12.6 % (27)	14.8 % (4)	63.0 % (17)	44.4 % (12)

Patients could have more than one MRB

W. R. Heizmann et al., *Infection* (2015)

Selezione di patogeni resistenti legati all'abuso /uso inappropriato delle diverse classi di antibiotici

- Cefalosporine di III generazione
  - MRSA, MRSE
  - VRE
  - Streptococco pneumoniae PR
  - Enterobacteriaceae ESBL +
  - Enterobacteriaceae AmpC +
  - Acinetobacter MDR
  - Clostridium difficile
- Fluorchinolonici
  - MRSA
  - Pseudomonas MDR
  - Enterobacteriaceae MDR (ESBL+)
  - Enterobacteriaceae AmpC+
  - Enterobacteriaceae FR
  - Colite da Clostridium difficile
- Carbapenemici
  - Stenotrophomonas maltophilia MDR
  - Acinetobacter baumannii MDR
  - Burkholderia cepacia MDR
  - Pseudomonas spp PAN-R
  - Klebsiella (Altri Enterobatteri) KPC+
  - Candidosi invasiva

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http://www.wjes.org/content/7/1/36

Table 4 Aerobic bacteria identified in peritoneal fluid

Total		**1,525 (100%)**
Aerobic Gram-negative bacteria		**1,041 (69.2%)**
Escherichia coli		632 (41.4%)
(Escherichia coli resistant to third generation cephalosporins)	64/632(**10**%)	64 (4.2%)
Klebsiella pneuumoniae		109 (7.1%)
(Klebsiella pneumoniae resistant to third generation cephalosporins)	37/109(**34**%)	37 (2.4%)
Enterobacter		63 (4.1%)
Proteus		33 (2.1 %)
Pseudomonas		80 (5.2%)
Others		124 (8.1%)
Aerobic Gram-positive bacteria		**484 (31.7%)**
Enterococcus faecalis		169 (11%)
Enterococcus faecium		72 (4.7%)
Staphylococcus Aureus		56 (3.7%)
Streptococcus spp.		100 (6,6%)
Others		87 (5.7%)

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http://www.wjes.org/content/7/1/36

	Community-acquired Isolates n°	Healthcare-associated Isolates n°
Aerobic bacteria	988 (100%)	567 (100%)
Escherichia coli	480 (48.6%)	152 (26.8%)
(Escherichia coli resistant to third generation cephalosporins)	30 (3%)	34 (6%)
Klebsiella pneumoniae	52 (5.2%)	57 (10%)
(Klebsiella pneumoniae resistant to third generation cephalosporins)	11 (1,7%)	22 (6.7%)
Pseudomonas	42 (4.2%)	38 (6.7%)
Enterococcus faecalis	78 (7.9%)	91 (16%)
Enterococcus faecium	39 (3.9%)	43 (7.6%)

30/480(**6**%)

34/152(**22**%)

11/52(**21**%)

22/57(**39**%)

Di Carlo *et al. BMC Anesthesiology* 2013, **13**:13
http://www.biomedcentral.com/1471-2253/13/13

BMC Anesthesiology

RESEARCH ARTICLE Open Access

KPC - 3 *Klebsiella pneumoniae* ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients

Paola Di Carlo[1*], Gaspare Gulotta[2], Alessandra Casuccio[3], Gianni Pantuso[4], Maurizio Raineri[5], Clizia Airò Farulla[4], Sebastiano Bonventre[2], Giuliana Guadagnino[1], Daniela Ingrassia[1], Gianfranco Cocorullo[2], Caterina Mammina[1] and Antonino Giarratano[5]

Table 1 Characteristics of 30 post-abdominal surgical ICU with infection by KPC-3 *Klebsiella pneumoniae* ST258 clone

Patients (age yrs, gender)	Source of KPC-Kp positive isolate	Surgical infection	Underlying disease	Treatment	Outcome
01. 22, F	BAL[1], Intraoperative Sample	SSI [2]	Crush Syndrome	T + C[3]	Survived
02. 66, M	Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	HDT + C[4]	Survived
03. 54, F	Percutaneous Fluid	Pancreatic Abscess	Chronic Pancreatitis	HDT + C	Survived
04. 61, M	Intraoperative Sample	Intra-abdominal Abscess	Crohn's Disease	HDT + C	Survived
05. 68, M	BAL, Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	HDT + C	Survived
06. 60, F	Percutaneous Fluid	Liver Abscess	Liver Cancer	HDT + C	Survived
07. 61, F	Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	HDT + C	Survived
08. 75, F	Drainage Fluid	Perianal Abscess	Rectal Cancer	HDT + C	Survived
09. 55, F	Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	HDT + C	Survived
10. 57, F	Drainage Fluid	Perineal Abscess	Rectal Cancer	HDT + C	Survived
11. 53, M	BAL, Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	T + C	Died
12. 67, F	Intraoperative Sample	Intra-abdominal Abscess	Colon Cancer	HDT + C	Survived
13. 56, M	Intraoperative Sample	Intra-abdominal Abscess	Crohn's Disease	HDT + C	Survived
14. 45, M	BAL, Intraoperative Sample	Intra-abdominal Abscess	Pancreatic Cancer	HDT + C	Died
15. 57, F	Percutaneous Fluid	Pancreatic Abscess	Chronic Pancreatitis	T + C	Survived
16. 20, M	Percutaneous Fluid	Liver Abscess	Liver Cancer	T + C	Survived
17. 45, M	BAL, Wound Sample	SSI	Gastric By Pass	T + C	Died
18. 55, M	BAL, Intraoperative Sample	Peritonitis	Peritonitis	T + C	Died
19. 56, F	BAL, Abdominal Drain	Anastomotic Leak	Rectal Cancer	T + C	Survived
20. 65, F	BAL, Abdominal Drain	Anastomotic Leak	Rectal Cancer	T + C	Died
21. 84, M	BAL, Abdominal Drain	Anastomotic Leak	Rectal Cancer	T + C	Died
22. 29, M	Abdominal Drain	Anastomotic Leak	Colorectal Cancer	T + C	Died
23. 59, M	Intraoperative Sample	Anastomotic Leak	Crohn's Disease	T + C	Survived
24. 61, M	BAL, Abdominal Drain	Anastomotic Leak	Colorectal Cancer	T + C	Died
25. 76, M	BAL, Intraoperative Sample	Peritonitis	Peritonitis	T + C	Died
26. 79, M	BAL, Abdominal Drain	Anastomotic Leak	Rectal Cancer	T + C	Died
27. 52, F	BAL, Wound Sample	SSI	Gastric By Pass	T + C	Died
28. 51, F	BAL, Wound Sample	SSI	Thyroid Cancer	T + C	Died
29. 52, F	Intraoperative Sample	Peritonitis	Peritonitis	T + C	Survived
30. 62, M	BAL, Wound Sample	Anastomotic Leak	Rectal Cancer	T + C	Survived

[1]**BAL**: Bronchoalveolar Lavage; [2]**SSI**: Surgical Site Infection; [3] **T + C**: Tigecycline plus Colistin; [4]**HDT + C**: High Dose Tigecycline plus Colistin.

% ESBL +

2015
AUSL Ferrara Argenta Cento Delta/AOU S.Anna/LUP

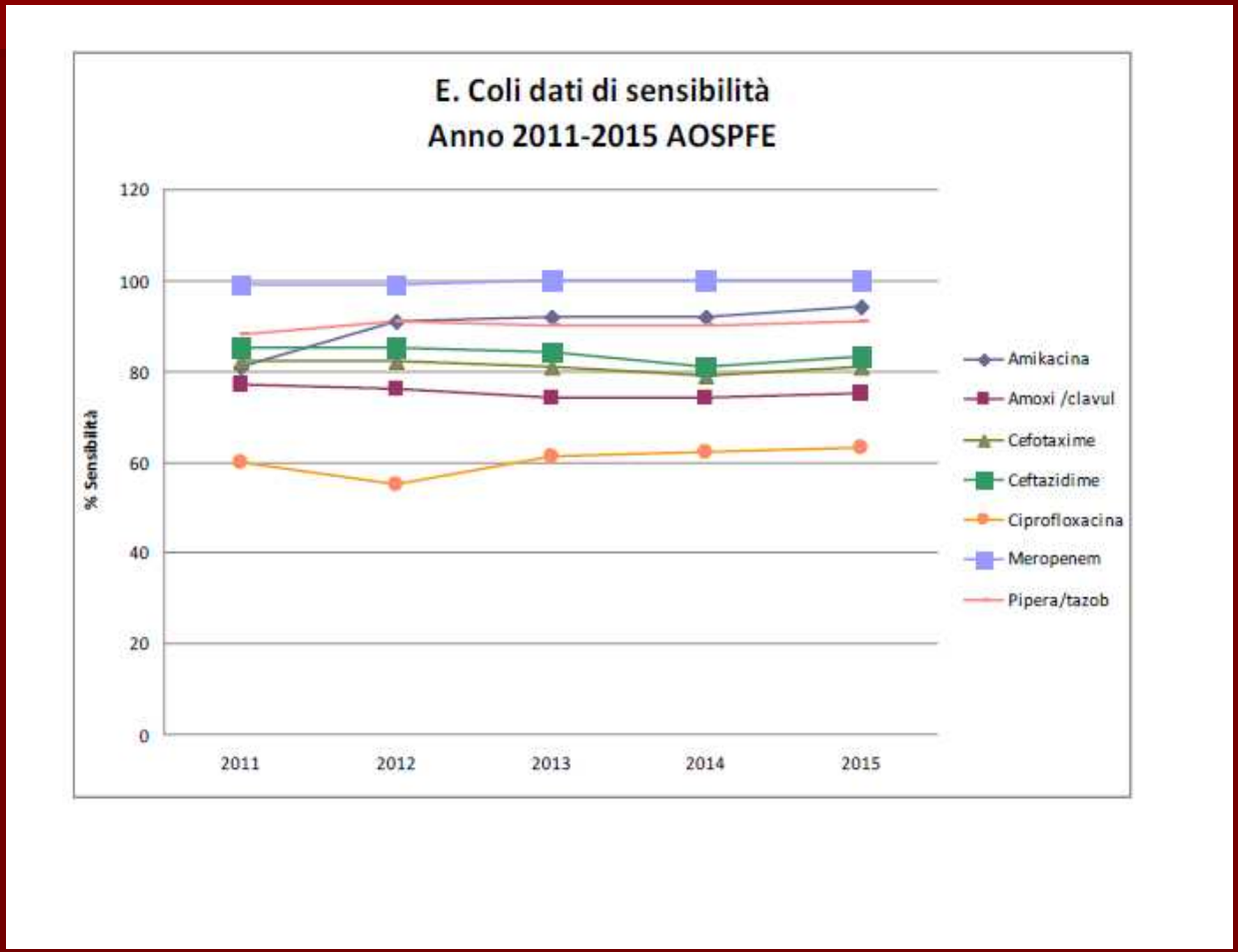
	Argenta 2015	Cento 2015	Delta 2015	AOU S.Anna	LUP 2015
E.coli	43	32	36	18	20
K.pneumoniae	52	49	46	21	26
P.mirabilis	36	27	24	22	23

M.Rita Rossi

UO Semplice di Microbiologia e Sierologia

AOU S.Anna Ferrara

E.Coli ESBL+ 2010>23% 2015>18%



Klebsiella ESBL+ : 2010>31%; 2015>22%

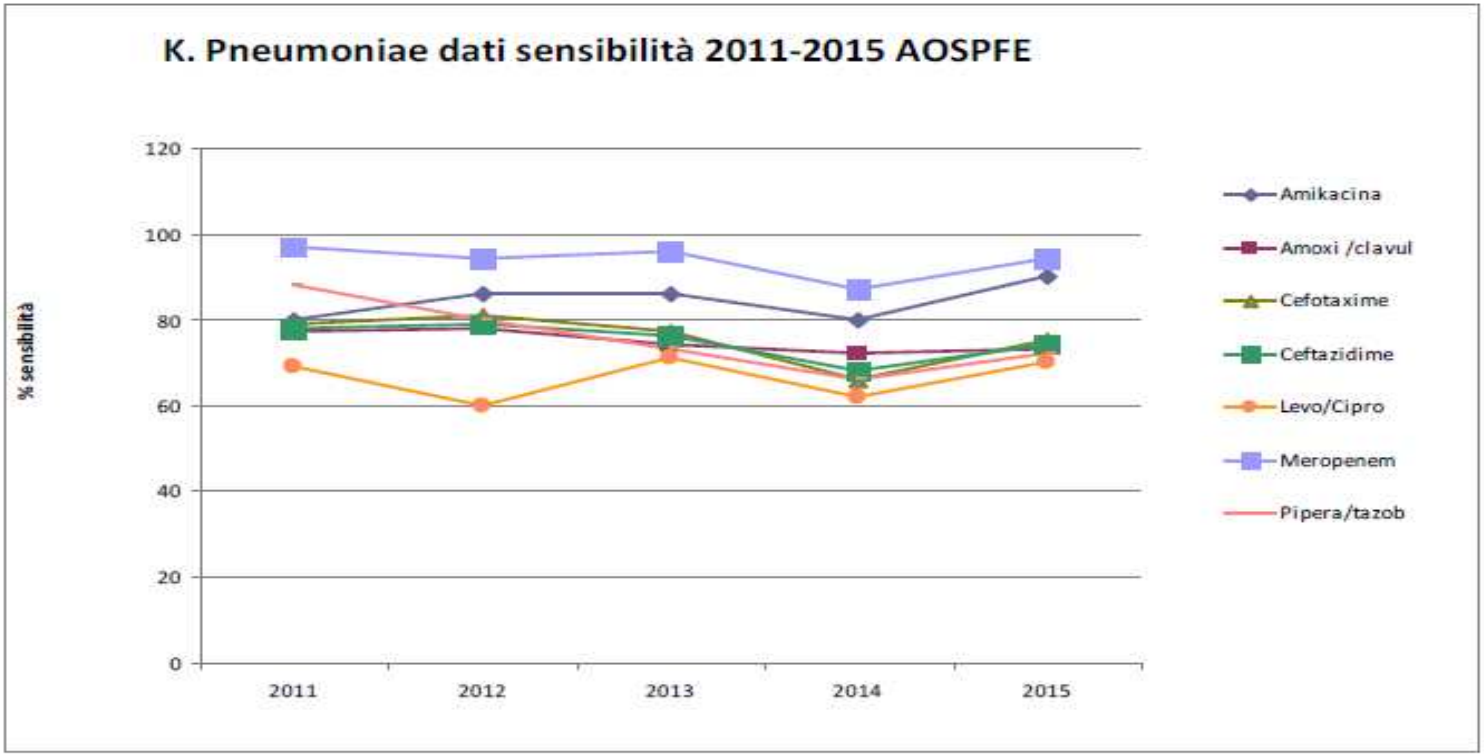


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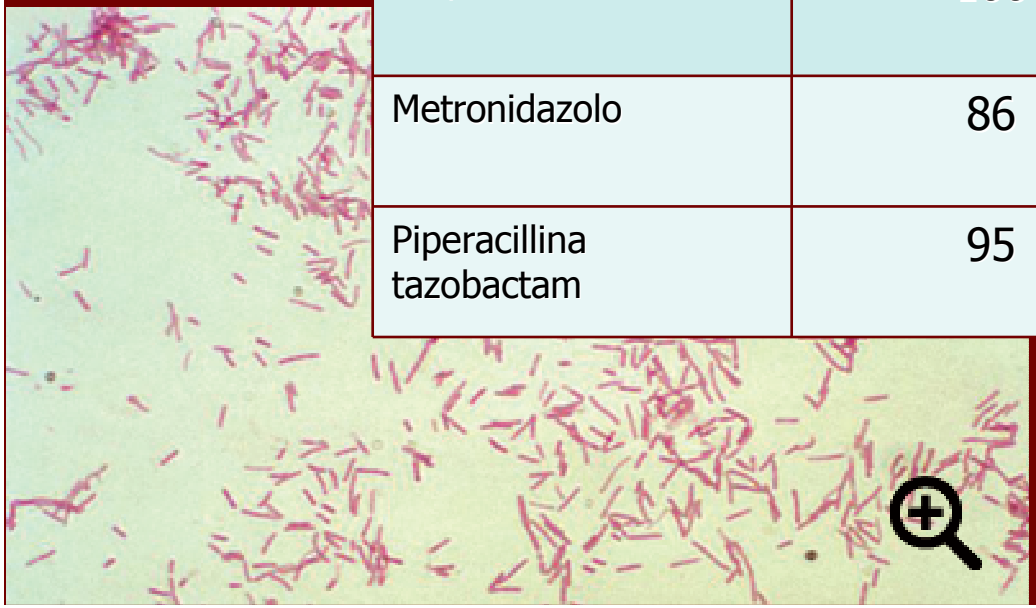
Table 6 Anaerobic bacteria identified in peritoneal fluid

Anaerobes	**197**
Bacteroides	126 (64%)
(Bacteroides resistant to Metronidazole)	4 (2%)
Clostridium	16 (8.1%)
(Clostridium resistant to Metronidazole)	1 (0.5%)
Others	55 (27.9%)

Bacteroides fragilis
Anno 2015

Bacteroides fragilis	**Ospedali AUSL FE** 23 ceppi Sensibilità %	**Ospedale Cona FE** 62 ceppi Sensibilità %
Clindamicina	68	70
Imipenem	100	98
Metronidazolo	86	88
Piperacillina tazobactam	95	91



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	Community-acquired Isolates n°	Healthcare-associated Isolates n°
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Enterococcus faecium	39 (3.9%)	43 (7.6%)

30/480(**6**%)

34/152(**22**%)

11/52(**21**%)

22/57(**39**%)

Copertura antibatterica per enterococco non indicata nelle forme comunitarie moderate Montravers 2015

R16 – Enterococci should probably not be taken into account in empirical antibiotic therapy for community-acquired IAI with no signs of severity.

(Grade 2–) STRONG agreement

Rationale: Enterococci are isolated in 5 to 20% of cases of community-acquired peritonitis. Their pathogenicity remains controversial, but they could be responsible for excess morbidity (higher rate of extraperitoneal postoperative infectious complications and intraperitoneal abscess formation), while their impact on mortality remains hypothetical [4,7,27,38–40]. There is no formal evidence to justify taking enterococci into account in the choice of empirical antibiotic therapy, except in targeted populations such as elderly or immunodepressed subjects [39,40].

Enterococcus faecalis anno 2015

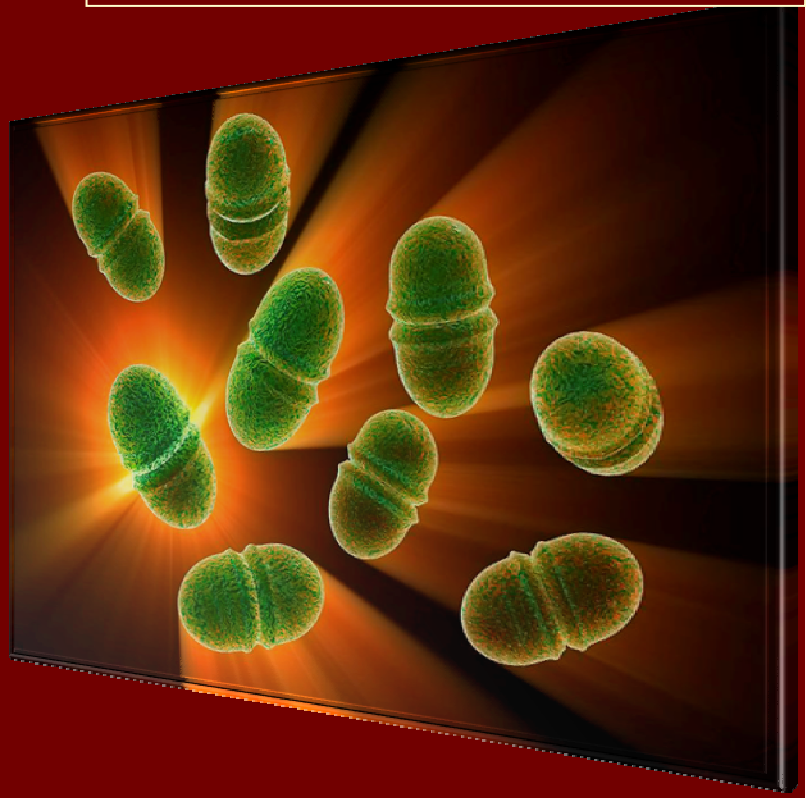
	Ospedali AUSL FE 104 ceppi	Ospedale Cona FE 536 ceppi
Ampicillina	99	99
Ampicillina sulbactam	99	99
Gentamicina 500	50	52
Imipenem	98	99
Levofloxacina*	54	63
Linezolide	100	100
Nitrofurantoina*	100	99
Teicoplanina	100	100
Tigeciclina	100	100
Vancomicina	100	100

Enterococcus resistenze naturali:
- Tutte le cefalosporine
- Clindamicina
- Cotrimoxazolo
- Aminoglicosidi a potenza normale

Enterococcus faecium anno 2015

*EUCAST 2015 indica utilità del saggio solo per IVU non complicate

	LUP FE 173 ceppi Sensibilità %
Ampicillina	14
Ampicillina sulbactam	14
Gentamicina 500	44
Imipenem	13
Levofloxacina*	18
Linezolide	98
Teicoplanina	98
Tigeciclina	99
Vancomicina	96



Enterococcus faecium 6 ceppi /173 (3.6%) vanco R isolati da urine

Enterococcus resistenze naturali:
- Tutte le cefalosporine
- Clindamicina
- Cotrimoxazolo
- Aminoglicosidi a potenza normale

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Table 7 Candida isolates identified in peritoneal fluid

Candida	**138**
Candida albicans	110 (79.7%)
(Candida albicans resistant to Fluconazole)	4 (2.9%)
Non-albicans Candida	28 (20.3%)
(non-albicans Candida resistant to Fluconazole)	5 (3.6%)

Enterobatteri CRE 2014/2015

PAZIENTI COINVOLTI
(isolati da campioni clinici)

AUSL Ferrara **55** pazienti / **AOU S.Anna FE 40 pazienti**

CRE	Argenta	Cento	Delta	Quisisana	Salus	RSA	Centri prelievo	AOU S.Anna	LUP
2014	2	1	7	2	1	0	8	17	38
2015	3	5	19	2	0	4	22	40	95

PAZIENTI Emocoltura Pos	AUSL	AUSL HODGE-CRE	AOU FE	AOU FE HODGE-CRE
2014	0		1	
2015	4	1	9	3

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UO Semplice di Microbiologia e Sierologia
AOU S.Anna Ferrara

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- Forme comunitarie e associate alle cure sanitarie;
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- Considerare enterococco e candida ?
- Presenza d' infezioni/colonizzazioni da KPC;
- Regimi terapeutici senza carbapenemico

Appropriatezza della terapia antibiotica

- Spettro antimicrobico idoneo;
- Timing d'inizio della terapia adeguato;
- Grado di esposizione all'antibiotico nella sede d'infezione ottimale ;
- Appropriatezza del dosaggio;
- Modalità e frequenza di somministrazione idonea;
- Monitoraggio delle concentrazioni plasmatiche;
- Durata limitata alla risoluzione clinica;

Criteri per **ottimizzare la terapia antibiotica** delle infezioni gravi

Fattori legati al paziente

- Presenza di fattori rischio;
- Comorbosità;
- Presenza di allergie farmacologiche;
- Fisiopatologia dell' ospite;
- Pregressi trattamenti antibiotici;
- Colonizzazione;
- Precedenti infezioni

Fattori legati all' infezione

- Tipo d'infezione;
- Gravità della stessa;
- Sorgente dell'infezione (nella sepsi)
- Etiologia generale;
- Patterns nazionali e/o locali di sensibilità

Fattori legati allo antibiotico

- Spettro dell' antibiotico: ampio, comprese le forme MDR;
- Attività battericida;
- Potenza elevata con evidenza di efficacia clinica;
- Profilo farmacocinetico (PK) /farmacodinamico (PD) favorevole;
- Scarsa induzione di resistenze;
- Manegevolezza: effetti indesiderati ed interazioni farmacologiche;

Attività battericida degli antibiotici

Tempo dipendenti

Beta-lattamici
Glicopeptidi
Monobattamici
Oxazolidinoni
Macrolidi

Concentrazione-dipendenti

Aminoglicosidi
Fluorchinoloni
Rifampicina
Daptomicina
Glicilciclina

Correlazione PK/PD e PDI

T > MIC

AUC / MIC
Cmax / MIC

Mazzei T. 2010 modificata

Variazioni di dosaggio in presenza di pazienti con insufficienza renale o con iperfiltrazione glomerulare

Table 2 Recommended dosing regimens (according to renal function) of the most commonly used renally excreted antimicrobials [248]

	Renal function			
Antibiotic	**Increased**	**Normal**	**Moderately impaired**	**Severely impaired**
Piperacillin/tazobatam	16/2 g q24 h CI or 3.375 q6 h EI over 4 hours	4/0.5 g q6 h	3/0.375 g q6 h	2/0.25 g q6 h
Imipenem	500 mg q4 h or 250 mg q3 h over 3 hours CI	500 mg q6 h	250 mg q6 h	250 mg q12 h
Meropenem	1 g q6 h over 6 hours CI	500 mg q6 h	250 mg q6 h	250 mg q12 h
Ertapenem	ND	1 g q24 h	1 g q24 h	500 mg q24 h
Gentamycin	9 to 10 mg/kg q24 h[b]	7 mg/kg q24 h	7 mg/kg q36–48 h	7 mg/kg q48–96 h
Amikacin	20 mg/kg q24 h	15 mg/kg q24 h	15 mg/kg q36–48 h[b]	15 mg/kg q48–96 h
Ciprofloxacin	600 mg q12 h or 400 mg q8 h	400 mg q12 h	400 mg q12 h	400 mg q24 h
Levofloxacin	500 mg q12 h	750 mg q24 h	500 mg q24 h	500 mg q48 h
Vancomycin	30 mg/kg q24 h CI	500 mg q6 h	500 mg q12 h	500 mg q24–72 h
Teicoplanin	LD 12 mg/kg q12 h for 3 to 4 doses; MD 6 mg/kg q12 h	LD 12 mg/kg q12 h for 3 to 4 doses; MD 4 to 6 mg/kg q12 h	LD 12 mg/kg q12 h for 3 to 4 doses; MD 2 to 4 mg/kg q12 h	LD 12 mg/kg q12 h for 3 to 4 doses; MD 2 to 4 mg/kg q24 h
Tigecycline	LD 100 mg; MD 50 mg q12 h	LD 100 mg; MD 50 mg q12 h	LD 100 mg; MD 50 mg q12 h	LD 100 mg; MD 50 mg q12 h

WSES World J Emerg Surgery 2013

Anaesth Crit Care Pain Med 34 (2015) 117–130

SFAR
Société Française d'Anesthésie et de Réanimation

Guidelines

Guidelines for management of intra-abdominal infections

Philippe Montravers [a,*], Hervé Dupont [b], Marc Leone [c], Jean-Michel Constantin [d], Paul-Michel Mertes [e], and the Société française d'anesthésie et de réanimation (Sfar), Société de réanimation de langue française (SRLF), Pierre-Francois Laterre [f], Benoit Misset [g], Société de pathologie infectieuse de langue française (SPILF), Jean-Pierre Bru [h], Rémy Gauzit [i], Albert Sotto [j], Association française de chirurgie (AFC), Cecile Brigand [k], Antoine Hamy [l], Société française de chirurgie digestive (SFCD), Jean-Jacques Tuech [m]

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Conoscenza dei dati microbiologici locali

R11 – Empirical antibiotic therapy protocols for community-acquired IAI must be established on the basis of regular analysis of national and regional microbiological data in order to quantify and monitor the course of microbial resistance in the community.

(Grade 1+) STRONG agreement

Rationale: In view of the potential difficulty of selecting appropriate anti-infective therapy, local and regional antibiotic therapy protocols must be established on the basis of the community origin, patient characteristics (comorbidities), clinical severity, presence of documented beta-lactam allergy and by taking local bacterial resistance data into account [7,26–28]. These protocols must be elaborated by multidisciplinary teams (anaesthetists-intensive care physicians, microbiologists, surgeons, infectious disease specialists and pharmacists).

Conoscere profili di sensibilità Bacteroides spp

R13 – In view of the changing susceptibility profiles of *Bacteroides* spp., clindamycin and cefoxitin must not be used as empirical therapy in community-acquired IAI.

(Grade 1–) STRONG agreement

Rationale: More than 50% of *Bacteroides fragilis* strains have become resistant to cefoxitin, cefotetan (cephalosporin generally reserved for prophylaxis) and clindamycin. These agents can no longer be recommended for empirical therapy. The susceptibility of anaerobes to penicillins + inhibitors (amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, piperacillin/tazobactam), carbapenems (ertapenem, imipenem, meropenem) and nitroimidazoles (metronidazole) is preserved [7].

Terapia anticandida non contemplata nelle forme comunitarie moderate

R14 – Empirical therapy active against Candida should not be initiated in community-acquired IAI in the absence of signs of severity.

(Grade 1–) STRONG agreement

Rationale: The data of the literature show that it is unnecessary to institute empirical antifungal therapy for community-acquired peritonitis in the absence of signs of severity, except in immunodepressed patients, transplant recipients or patients with an inflammatory disease [34–36].

Terapia anticandida in presenza di paziente critico e fattori di rischio

R15 – Antifungal therapy should probably be initiated in severe peritonitis (community-acquired or postoperative), in the presence of at least 3 of the following criteria: haemodynamic failure, female gender, upper gastrointestinal surgery, antibiotic therapy for more than 48 hours.

(Grade 2+) STRONG agreement

Rationale: In severe peritonitis, the presence of yeasts is a factor of poor prognosis [8]. The presence of yeasts on direct examination of peritoneal fluid indicates the presence of a large inoculum and is associated with excess mortality [29]. Clinical features suggestive of yeast infection are haemodynamic failure, upper gastrointestinal perforation, female gender and antibiotic therapy during the previous 48 hours [37]. When 3 of these 4 criteria are present, the probability of isolating Candida in peritoneal fluid is 71%. No prospective study has formally validated the rationale for antifungal therapy. Nevertheless, in view of the clinical severity, it appears reasonable to initiate empirical antifungal therapy in this setting.

R20 – Piperacillin/tazobactam plus or minus gentamicin should probably be used in critically ill patients with community-acquired IAI.

(Grade 2+) STRONG agreement

Rationale: In the presence of septic shock or severe sepsis, inappropriate anti-infective therapy (not covering all of the microorganisms isolated) is regularly associated with increased morbidity and mortality [30,49,52]. The percentage susceptibility to amoxicillin/clavulanic acid (AMC) of *Enterobacteriaceae* isolated from adults with community-acquired peritonitis in France is > 75% of naturally susceptible strains, while 96 to 100% of strains are susceptible to piperacillin-tazobactam [7]. Combination antibiotic therapy is justified to extend the spectrum of activity in order to minimize the risk of therapeutic impasse (for example resistance of *E. coli* to amoxicillin/clavulanic acid). No study has specifically evaluated peritonitis associated with septic shock. Only one good quality study focusing on severe community-acquired intra-abdominal infections with severe sepsis failed to demonstrate any benefit of combination antibiotic therapy [53]. In the presence of septic shock, the addition of an aminoglycoside could ensure a broader spectrum of action.

Paziente critico con forma grave comunitaria o associata alle cure sanitarie : preferire echinocandina

R21 – When it is decided to prescribe empirical antifungal therapy in a critically ill patient with community-acquired or healthcare-associated IAI, an echinocandin should probably be used.

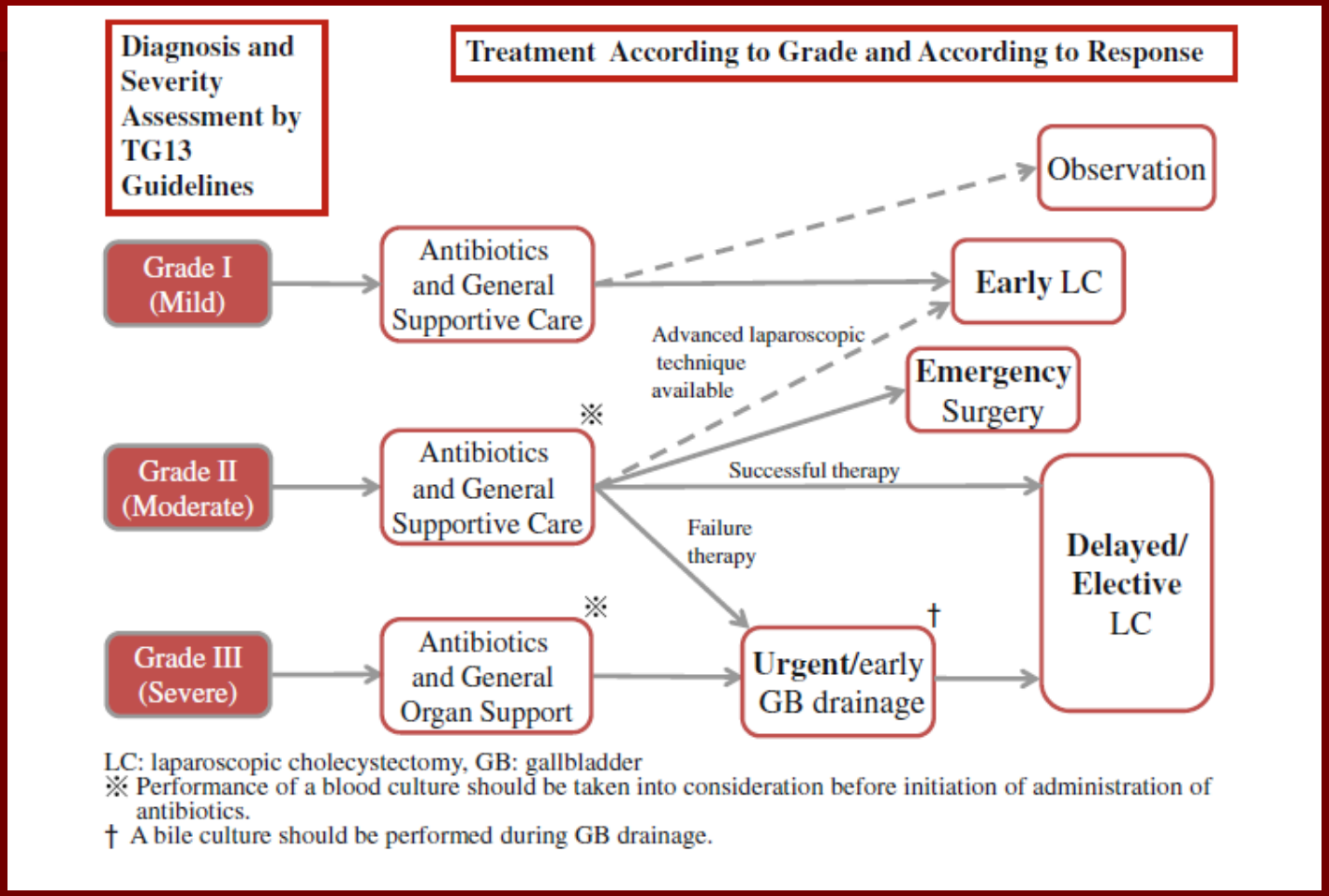
(Expert opinion) STRONG agreement

Rationale: The empirical antibiotic therapy strategy is based on identification of the species, local and regional epidemiology, history of recent treatment (3 months) with an azole antibiotic, clinical severity and known possible colonization. An echinocandin should be preferred in a critically ill patient, recent exposure to azole antibiotics (3 months) and the presence of risk factors for *C. glabrata* or *C. krusei* infection. First-line fluconazole therapy remains indicated in the other cases [54]. However, no study has specifically evaluated the efficacy of antifungal therapy in intra-abdominal infections.

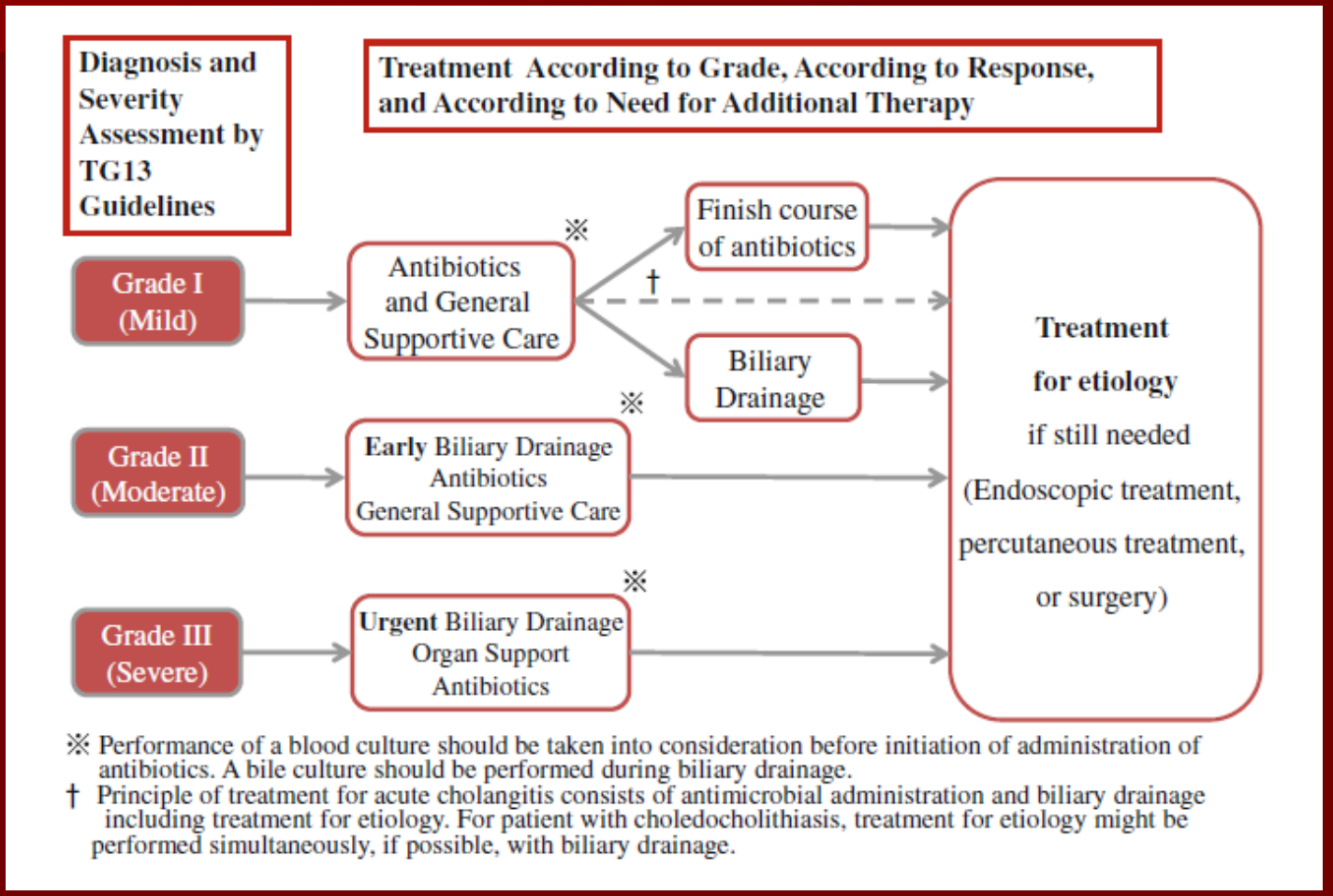
De – escalation dopo indentificazione dell' eziologia

R22 – In a patient treated for community-acquired or healthcare-associated IAI, antibiotic and antifungal therapy should probably be de-escalated after reception of the microbiology and mycology identification and susceptibility testing results (to adapt treatment in order to obtain the narrowest therapeutic spectrum).

Tokio Guidelines 2013 Algoritmo Colecistite



Tokio Guidelines 2013
Algoritmo colangite



Sartelli et al. World Journal of Emergency Surgery 2013, 8:3
http://www.wjes.org/content/8/1/3

WJES WORLD JOURNAL OF EMERGENCY SURGERY

REVIEW Open Access

2013 WSES guidelines for management of intra-abdominal infections

Massimo Sartelli[1*], Pierluigi Viale[2], Fausto Catena[3], Luca Ansaloni[4], Ernest Moore[5], Mark Malangoni[6], Frederick A Moore[7], George Velmahos[8], Raul Coimbra[9], Rao Ivatury[10], Andrew Peitzman[11], Kaoru Koike[12], Ari Leppaniemi[13], Walter Biffl[5], Clay Cothren Burlew[5], Zsolt J Balogh[14], Ken Boffard[15], Cino Bendinelli[14], Sanjay Gupta[16], Yoram Kluger[17], Ferdinando Agresta[18], Salomone Di Saverio[19], Imtiaz Wani[20], Alex Escalona[21], Carlos Ordonez[22], Gustavo P Fraga[23], Gerson Alves Pereira Junior[24], Miklosh Bala[25], Yunfeng Cui[26], Sanjay Marwah[27], Boris Sakakushev[28], Victor Kong[29], Noel Naidoo[30], Adamu Ahmed[31], Ashraf Abbas[32], Gianluca Guercioni[33], Nereo Vettoretto[34], Rafael Díaz-Nieto[35], Ihor Gerych[36], Cristian Tranà[37], Mario Paulo Faro[38], Kuo-Ching Yuan[39], Kenneth Yuh Yen Kok[40], Alain Chichom Mefire[41], Jae Gil Lee[42], Suk-Kyung Hong[43], Wagih Ghnnam[44], Boonying Siribumrungwong[45], Norio Sato[11], Kiyoshi Murata[46], Takayuki Irahara[47], Federico Coccolini[4], Helmut A Segovia Lohse[48], Alfredo Verni[49] and Tomohisa Shoko[50]

Appendix 3. Antimicrobial therapy for community-acquired extra-biliary IAIs in critically ill patients presenting with no ESBL-associated risk factors (WSES recommendations)

Community-acquired extra-biliary IAIs
Critically ill patients (≥ SEVERE SEPSIS)
No risk factors for ESBL

PIPERACILLIN/TAZOBACTAM
Daily schedule: 8/2 g LD then 16/4 g/day via continuous infusion or 4.5 g every 6 hours (4-hour infusion time)

Appendix 4. Antimicrobial therapy for community-acquired extra-biliary IAIs in critically ill patients presenting with ESBL-associated risk factors (WSES recommendations)

Community-acquired IAIs
Critically ill patients (≥ SEVERE SEPSIS)
ESBL-associated risk factors
MEROPENEM
Daily schedule: 500 mg every 6 hours (6-hour infusion time)
OR
IMIPENEM
Daily schedule: 500 mg every 4 hours (3-hour infusion time)
+/−
FLUCONAZOLE
Daily schedule: 600 mg LD then 400 mg every 24 hours (2-hour infusion time)

Appendix 10. Antimicrobial therapy for nosocomial IAI in critically ill patients. (WSES recommendations)

Hospital-acquired extra-biliary IAIs
Critically ill patients (≥SEVERE SEPSIS)
Risk factors for MDR pathogens
PIPERACILLIN
Daily schedule: 8 g by LD then 16 g via continuous infusion or 4 g every 6 hours (4-hour infusion time)
+
TIGECYCLINE
Daily schedule: 100 mg LD then 50 mg every 12 hours (2-hour infusion time)
+
ECHINOCANDIN
caspofungin (70 mg LD, then 50 mg daily),
anidulafungin (200 mg LD, then 100 mg daily),
micafungin (100 mg daily)
OR
MEROPENEM
Daily Schedule: 500 mg every 6 hours (6-hour infusion time)
IMIPENEM
Daily Schedule: 500 mg every 4 hours (3-hour infusion time)
DORIPENEM
Daily Schedule: 500 mg every 8 hours (4-hour infusion time)
+
TEICOPLANIN
Daily Schedule: LD 12 mg/kg/12 h for 3 doses then 6 mg/kg every 12 hours (with TDM corrections/ adjustments – PD target 20–30 mg/L)
+
ECHINOCANDIN
caspofungin (70 mg LD, then 50 mg daily),
anidulafungin (200 mg LD, then 100 mg daily),
micafungin (100 mg daily)

Antibiotic Guidelines 2015-2016

Treatment Recommendations For Adult Inpatients

Also available online at insidehopkinsmedicine.org/amp

JOHNS HOPKINS MEDICINE

Pancreatitis

TREATMENT

- Antibiotic prophylaxis is NOT indicated in patients with severe acute pancreatitis (SAP), including those with sterile pancreatic necrosis.
- Antimicrobial therapy has no effect on morbidity and mortality, and prophylactic antibiotics have been associated with a change in the spectrum of pancreatic isolates from enteric Gram-negatives to Gram-positive organisms and fungi.
- Infected pancreatic necrosis is defined by CT scan with gas in the pancreas and/or percutaneous or surgical specimen with organisms evident on gram stain or culture. Therapy should be directed based on culture results.
- In patients presenting with suspected abdominal sepsis, consider empiric therapy:
  - Piperacillin-tazobactam 4.5 g IV Q6H

    OR
  - Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H

    OR
  - Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H

INFEZIONI INTRADDOMINALI

La definizione di infezione intraddominale risponde ad almeno uno dei criteri

1. Isolamento colturale di *Klebsiella pneumoniae* KPC da pus prelevato in corso di intervento chirurgico o agoaspirato (drenaggio eco/TC guidato).
2. Presenza, senza altre cause, di almeno due tra
   - febbre
   - nausea/vomito
   - addominoalgie
   - ittero

   E

   almeno uno tra :

- Isolamento colturale di *Klebsiella pneumoniae* KPC da drenaggi posizionati chirugicamente (es. Drenaggi in aspirazione a circuito chiruso, tubi a T)
- Isolamento colturale di *Klebsiella pneumoniae* KPC da emocolture E evidenza strumentale di infezione (Rx addome, ecografia, TC, RMN, scintigrafia)

Terapia empirica in attesa di antibiogramma

COLISTINA ev	9 MU dose da carico
	poi 4,5 MU ogni 12 ore
+	
TIGECICLINA ev	100-200 mg prima dose
	poi 100 mg ogni 12 ore
+	
MEROPENEM ev	2g in un'ora
	poi 2 g ogni 8 ore da infondere in 6 ore (6g/die)

Durata: 14 giorni, salvo complicanze

Sepsi di origine biliare da KPC

- Meropenem 2 g e.v.(in infusione prolungata per 6 ore) x 4 al giorno + Tigeciclina 100 mg x 2 e.v. /die (dose carico 200 mg e.v.) + Colistina 4,5 milioni x 2 e.v. / al dì dopo dose carico di 9 milioni ;

CANDIDOSI ADDOMINALE

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

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ORIGINAL

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A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality

Initial antifungal agent (%)	
Echinocandin	203 (63.8)
Azole/triazole	102 (32)
Amphotericin B	13 (4)
Adequate antifungal treatment (%)	283 (58.8)
Adequate source control (%)	335 (69.6)

VIII. What Is the Treatment for Intra-abdominal Candidiasis?

Recommendations

54. Empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis *(strong recommendation; moderate-quality evidence)*.
55. Treatment of intra-abdominal candidiasis should include source control, with appropriate drainage and/or debridement *(strong recommendation; moderate-quality evidence)*.
56. The choice of antifungal therapy is the same as for the treatment of candidemia or empiric therapy for nonneutropenic patients in the ICU (See sections I and V) *(strong recommendation; moderate-quality evidence)*.
57. The duration of therapy should be determined by adequacy of source control and clinical response *(strong recommendation; low-quality evidence)*.

Linee Guida : i quesiti

- Forme comunitarie e associate alle cure sanitarie;
- Paziente critico e stabile ;
- Impatto epidemiologico degli enterobatteri ESLB positivi ;
- Localizzazione intestinale o biliare ;
- Quando considerare enterococco, pseudomonas e candida ?
- Presenza d' infezioni/colonizzazioni da KPC;
- **Durata della terapia antibiotica ?**
- Regimi terapeutici alternativi senza carbapenemico nelle forme MDR

Terapia breve nelle forme localizzate comunitarie (<5 gg)

R23 – Antibiotic therapy should probably be administered for 2 to 3 days in localized community-acquired IAI.

(Grade 2+) STRONG agreement

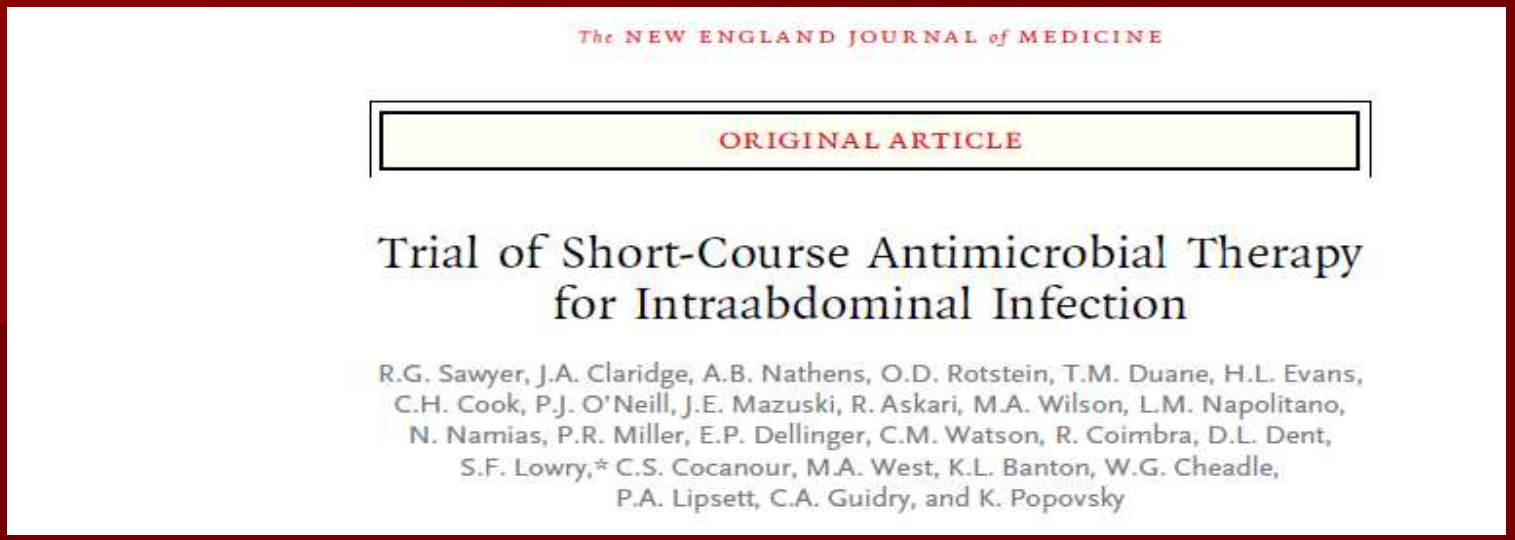
Rationale: The great majority of guidelines concerning the duration of antibiotic therapy are based on studies with low levels of evidence and expert opinions. In mild-to-moderate community-acquired peritonitis, there are many arguments in favour of brief antibiotic therapy ($<$ 5 days). This duration must be adapted to the degree of contamination observed intraoperatively and optimal surgical infection source control must be ensured. Most of the studies supporting these guidelines are now old and comprised a large proportion of appendicular infections [58]. However, these findings were supported by a randomized trial published in 2007 that concluded that a shorter duration of ertapenem (3 days) was as effective as treatment for $\geq$ 5 days in mild-to-moderate community-acquired peritonitis [59].

Durata 5 – 7 gg forme severe

R24 – Antibiotic therapy should probably be administered for 5 to 7 days in generalized community-acquired IAI.

(Grade 2+) STRONG agreement

Rationale: The optimal duration of treatment for serious community-acquired peritonitis has not been established and is only based on expert opinions. This duration probably depends on the patient's comorbidities, the severity of organ failures, the time to return of bowel movements and the quality of the surgical procedure. Prospective studies need to be conducted on this subject. Return of bowel movements, return to apyrexia, lowering of the leukocyte count and correction of organ failures are criteria classically used to evaluate the efficacy of treatment [59–61].



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky

Terapia antibiotica di 4 o 10 giorni efficacia sovrapponibile

Outcome primario

% infezioni della ferita chirurgica, recidiva IAI, morte a 30 gg

Table 2. Primary and Major Secondary Outcomes.*

Variable	Control Group (N=260)	Experimental Group (N=257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99
Time to event — no. of days after index source-control procedure			
Diagnosis of surgical-site infection	15.1±0.6	8.8±0.4	<0.001
Diagnosis of recurrent intraabdominal infection	15.1±0.5	10.8±0.4	<0.001
Death	19.0±1.0	18.5±0.5	0.66
Secondary outcome			
Surgical-site infection or recurrent intraabdominal infection with resistant pathogen — no. (%)	9 (3.5)	6 (2.3)	0.62
Site of extraabdominal infection — no. (%)			
Any site†	13 (5.0)	23 (8.9)	0.11
Urine	10 (3.8)	13 (5.1)	0.65
Blood	3 (1.2)	5 (1.9)	0.71
Lung	3 (1.2)	3 (1.2)	0.99
Area of skin other than surgical site	1 (0.4)	4 (1.6)	0.36
Vascular catheter	0 (0)	2 (0.8)	0.47
Clostridium difficile infection — no. (%)	3 (1.2)	5 (1.9)	0.71
Extraabdominal infection with resistant pathogen — no. (%)	6 (2.3)	2 (0.8)	0.29
Duration of outcome — days			
Antimicrobial therapy for index infection			<0.001
Median	8	4	
Interquartile range	5–10	4–5	
Antimicrobial-free days at 30 days			<0.001
Median	21	25	
Interquartile range	18–25	21–26	
Hospitalization after index procedure			0.48
Median	7	7	
Interquartile range	4–11	4–11	
Hospital-free days at 30 days			0.22
Median	23	22	
Interquartile range	18–26	16–26	

* Plus–minus values are means ±SE.
† Some patients had extraabdominal infections at more than one site.

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

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Background. Increasing antimicrobial resistance among pathogens causing complicated intra-abdominal infections (cIAIs) supports the development of new antimicrobials. Ceftolozane/tazobactam, a novel antimicrobial therapy, is active against multidrug-resistant *Pseudomonas aeruginosa* and most extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae.

Methods. ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections) was a prospective, randomized, double-blind trial. Hospitalized patients with cIAI received either ceftolozane/tazobactam (1.5 g) plus metronidazole (500 mg) every 8 hours or meropenem (1 g) every 8 hours intravenously for 4–14 days. The prospectively defined objectives were to demonstrate statistical noninferiority in clinical cure rates at the test-of-cure visit (24–32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a noninferiority margin of 10%. Microbiological outcomes and safety were also evaluated.

Results. Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) endpoints, meeting the prespecified noninferiority margin. In patients with ESBL-producing Enterobacteriaceae, clinical cure rates were 95.8% (23/24) and 88.5% (23/26) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and 100% (13/13) and 72.7% (8/11) in patients with CTX-M-14/15 ESBLs. The frequency of adverse events (AEs) was similar in both treatment groups (44.0% vs 42.7%); the most common AEs in either group were nausea and diarrhea.

Conclusions. Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by multidrug-resistant pathogens.

Clinical Trials Registration. NCT01445665 and NCT01445678.

Ceftolozane/Tazobactam

- Nuova combinazione di una cefalosporina antipseudomonas e un inibitore della beta-lattamasi;
- Inibisce la formazione della parete cellulare batterica legandosi alle proteine leganti la penicillina (PBP);
- Tazobactam inibisce irreversibilmente l'attività di molte penicillinasi e cefalosporinasi;
- Attività in vitro contro molti organismi gram-negativi es. *Enterobacteriaceae ESBL* e *Pseudomonas aeruginosa PDR;*
- Indicazioni : Infezioni intraaddominali complicate, in combinazione con metronidazolo;
- Infezioni urinarie, incluso le pielonefriti;

Ceftazidime-Avibactam (Avycaz)

For the Treatment of Complicated Intra-Abdominal and Urinary Tract Infections

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Table 2 Aerobic, Gram-Negative Bacteria Effectively Targeted By Avycaz[8]

Complicated Intra-Abdominal Infections
• *Escherichia coli*
• *Enterobacter cloacae*
• *Klebsiella pneumoniae*
• *K. oxytoca*
• *Proteus mirabilis*
• *Pseudomonas aeruginosa*
• *Citrobacter freundii* complex

Table 1 Recommended Avycaz Dosage Regimen[8]

Estimated CrCl (mL/min)[a]	Recommended Dosage Regimen[b]
> 50	2.5 g every eight hours
31–50	1.25 g every eight hours
16–30	0.94 g every 12 hours
6–15[c]	0.94 g every 24 hours
≤ 5[c]	0.94 g every 48 hours

CrCl = creatinine clearance.

[a] As calculated using the Cockcroft-Gault formula

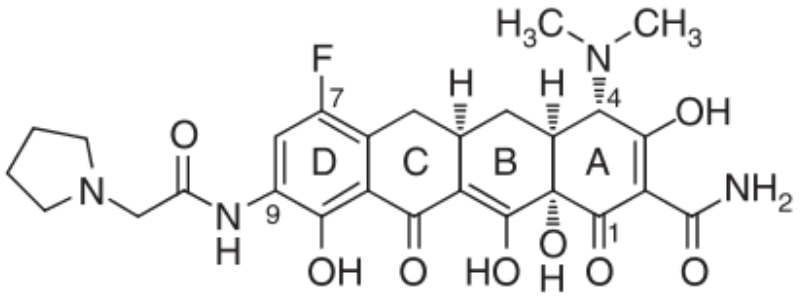
[b] All doses of Avycaz are administered by intravenous infusion over two hours.

[c] Both ceftazidime and avibactam are hemodialyzable; thus, administer Avycaz after hemodialysis on hemodialysis days.

Eravacycline for the treatment of intra-abdominal infections

Expert Opin. Investig. Drugs (2014) **23**(11):1575-1584

Box 1. Drug summary.

Drug name	Eravacycline
Phase	III
Indication	Intra-abdominal infection
Pharmacology description	Protein 30S ribosomal subunit inhibitor
Route of administration	Injectable/Oral
Chemical structure	
Pivotal trial(s)	[43,44,57,59]

Conclusioni

- Le infezioni intraddominali rimangono un' importante causa di morbilità e mortalità;
- Queste infezioni possono essere determinate sia da germi gram negativi che da anaerobi, ma spesso riconoscono una eziologia polimicrobica;
- Patogeni MDR, come gli enterobatteri ESBL+ e gli enterococchi gentamicina resistenti, sono frequentemente implicati;

Conclusioni II°

- E’ importante utilizzare, tempestivamente, antibiotici con una buona attività battericida, un’adeguata cinetica distrettuale e spettro allargato anche sulle forme MDR;
- Le forme da candida appaiono in aumento nei setting associati alle cure sanitarie, per cui non vanno sottovalutate e contemplate nel regime terapeutico, nel paziente critico;
- Ai fini prognostici rimane fondamentale il rapido controllo della sorgente infettiva ed il supporto intensivistico, in particolare nel paziente critico con sepsi grave o shock settico.