Diagnosi e Gestione clinica della Sepsi: Malattia Invasiva Meningococcica

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Il sottoscritto Carlo Tascini
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Astra*
- *Merck*
- *Pfizer*
- *Astellas*
- *Angelini*
- *Gilead*
- *Novartis.*
- *Biotest*
- *Thermofischer*



Bebe Vio posa per Anne Geddes per il vaccino contro la meningite

Caso clinico

- Giovane madre di 21 anni, in buona salute
- Figliola di 2 anni in buona salute
- 11 febbraio 2018 brividi e febbre assume tachipirina
- Inizia dolore intenso al dito medio mano destra con II e III falange fredde e bianche
- Accesso a PS periferico ore 18
- PA 100/60, FC 90 RITMICO, FR 20/MIN, SAT 96%
- QSOFA: 0

Caso clinico

- Al PS numerose lesioni tipo porpora agli arti superiori ed inferiori
- Febbre elevata
- Viene valutata e consigliato esame doppler arterioso e venoso arti superiori

CASO CLINICO



Caso clinico





Caso clinico

- La paziente alle 2 di notte del 12 febbraio viene portata all'Ospedale Cardarelli
- Al pronto soccorso viene riconosciuta come porpora fulminante ed inviata al Cotugno

All’ingresso al cotugno: 12 ore dal precedente accesso ospedaliero



All’ingresso al cotugno: 12 ore dal precedente accesso ospedaliero



- All’Ospedale Cotugno
- Ricovero in UTI
- Sedata ed intubata
- Desametasone, Rifampicina, Ceftriaxone 2 g, IGAM 5 ml/kg in infusione continua per i primi tre giorni

- Rachicentesi con film array positiva per meningococco
- Sierotipo molecolare: Gruppo C
- Ceppo inviato all'ISS: C St type 11, P1.5,-1.,10-8:F3-6,
- Ceppo dell'epidemia toscana

Esito dito medio mano destra



Esito mano sinistra



Esiti tardivi a 2 mesi: escara



Esiti tardivi a 2 mesi: escara



Intervento



2018: *N. meningitidis* gruppo W
bambina di 12 mesi, deceduta dopo cortisone ed antibiotico: endotossina 1,2, PCT 100



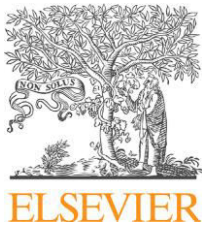
Increased incidence of invasive meningococcal disease of serogroup C / clonal complex 11, Tuscany, Italy, 2015 to 2016

P Stefanelli [1], A Miglietta [2], P Pezzotti [1], C Fazio [1], A Neri [1], P Vacca [1], F Voller [3], FP D'Ancona [4,5], R Guerra [5], S Iannazzo [5], MG Pompa [5], G Rezza [1]

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4. National Center for Epidemiology, Surveillance and Health Promotion - Istituto Superiore di Sanità, Rome, Italy
5. Ministry of Health, Directorate-General of health prevention, Rome, Italy

We report an increase of serogroup C *Neisseria meningitidis* invasive meningococcal disease in Tuscany. From January 2015 to end February 2016, 43 cases were reported, among which 10 were fatal, compared to two cases caused by serogroup C recorded in 2014 and three in 2013. No secondary cases occurred. Thirty–five strains belonged to C:P1.5–1,10–8:F3–6:ST-11(cc11). Control measures have been adopted and immunisation campaigns implemented. Studies on risk factors and carriage are ongoing.

Journal of Infection (2016) xx, 1–4



LETTER TO THE EDITOR

Clinical presentation and outcome of twenty cases of Invasive Meningococcal Disease due to Serogroup C – Clonal complex 11 in the Florence province, Italy, 2015–2016

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Table 1 Demographical and clinical characteris
ical presentation, from January 2015 to June 20

Characteristics (n available data/total)[a]	All patients (20 cases)	Septic shock with *Purpura fulminans* (9 cases)
Male sex (%, 20/20)	55%	66%
Years (mean, 20/20)	40 (13–83)	39 (13–83)
Main presenting symptoms (20/20)	Fever (Mean 38.7 °C) and petechiae (different degrees) always present	Confluent petechiae, fever
		22
Hours between symptoms onset and referral to ED (mean, 13/20)	24	1,5
MEWS score at presentation to ED (mean, 13/20)	1,8	
Selected bio-chemistry parameters		
White blood cells (mean, 16/20)	$13,1 \times 10^3$	$6,3 \times 10^3$
Platelets (mean, 16/20)	119×10^3	68×10^3
C-reactive protein (mean, 14/20)	18	11
Procalcitonin (mean, 10/20)	80	127
Cerebrospinal fluid		
Proteins (mean, 13/13)		30 (20–40)[b]
Cells (mean, 13/13)		5 (2–8)[b]
Glucose (mean, 13/13)		55 (50–65)[b]
Need for intensive care (IC) (20/20)	17/20	9/9
Mean length of stay in IC (days)		Not calculable[c]
Letality (20/20)	7/20; 35%	7/9; 77%

TAB 02. Malattie invasive da *N. meningit*
Anno 2015)

	Malattie in	
	Popolazione al 01/01/2014	*Neisseria meningitidis*
Abruzzo	1331574	4
Basilicata	576619	1
Calabria	1976631	1
Campania	5861529	10
Emilia-Romagna	4450508	14
Friuli V. Giulia	1227122	2
Lazio	5892425	24
Liguria	1583263	2
Lombardia	10002615	34
Marche	1550796	2
Molise	313348	0
P.A. Bolzano	518518	5
P.A. Trento	537416	3
Piemonte	4424467	9
Puglia	4090105	12
Sardegna	1663286	4
Sicilia	5092080	13
Toscana	3752654	38
Umbria	894762	4
Valle d'Aosta	128298	2
Veneto	4927596	12
TOTALE	60795612	**196**

TAB 01. Malattie invasive da
Anno 2016 (dati parziali, ag

	N
	Neisseria meningitidis
Abruzzo	3
Basilicata	2
Calabria	3
Campania	16
Emilia-Romagna	13
Friuli V. Giulia	2
Lazio	18
Liguria	3
Lombardia	29
Marche	5
Molise	0
P.A. Bolzano	1
P.A. Trento	1
Piemonte	14
Puglia	7
Sardegna	5
Sicilia	8
Toscana	35
Umbria	0
Valle d'Aosta	1
Veneto	12
TOTALE	**178**

Vaccine 36 (2018) 5962–5966

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journal homepage: www.elsevier.com/locate/vaccine

Invasive Meningococcal Disease due to group C N. meningitidis ST11 (cc11): The Tuscany cluster 2015–2016

Francesco Menichetti [a,⇑], Simona Fortunato [a], Andrea Ricci [a], Francesca Salani [a], Andrea Ripoli [b], Carlo Tascini [c], Francesco Maria Fusco [d], Jessica Mencarini [e], Alessandro Bartoloni [e], Massimo Di Pietro [f]

Table 2
Patient outcome according to demographic, clinical and management variables.

	Recovered (n = 38)	Sequelae or death (n = 15)	P value univariate analysis	OR[b]
Males	17 (45%)	9 (60%)	0.486	–
Mean age (range)	33.9 (3–70)	35.5 (17–75)	0.799	**1.003**
Previous Vaccination[a]	9 (24%)	2 (13%)	0.645	–
Meningitis	6 (16%)	2 (13%)	1	–
Meningitidis + meningococcemia	16 (42%)	7 (47%)	1	–
Meningococcemia	16 (42%)	6 (40%)	1	–
Septic shock	**14 (37%)**	**12 (80%)**	**0.011**	**1.211**
Multi-organ failure	11 (29%)	8 (53%)	0.177	–
Disseminate intravascular coagulophaty	**7 (18%)**	**9 (60%)**	**0.008**	**–**
Purpura fulminans	**6 (16%)**	**9 (60%)**	**0.004**	**6.641**
Adequate Antibiotic therapy	38 (100%)	15 (100%)	**1**	**–**
Steroid treatment	28 (74%)	11 (74%)	1	–
Pentaglobin®	8 (21%)	2 (13%)	0.797	–
ICU	25 (66%)	14 (93%)	0.089	–
Tertiary-care Universitary Hospital	**13 (34%)**	**0 (0%)**	**0.024**	**0.111**

[a] Previous receipt of a serogroup C-containing meningococcal conjugate vaccine.
[b] OR were calculated with a multivariate analysis on a total of 53 patients with the availability of all the listed variables.

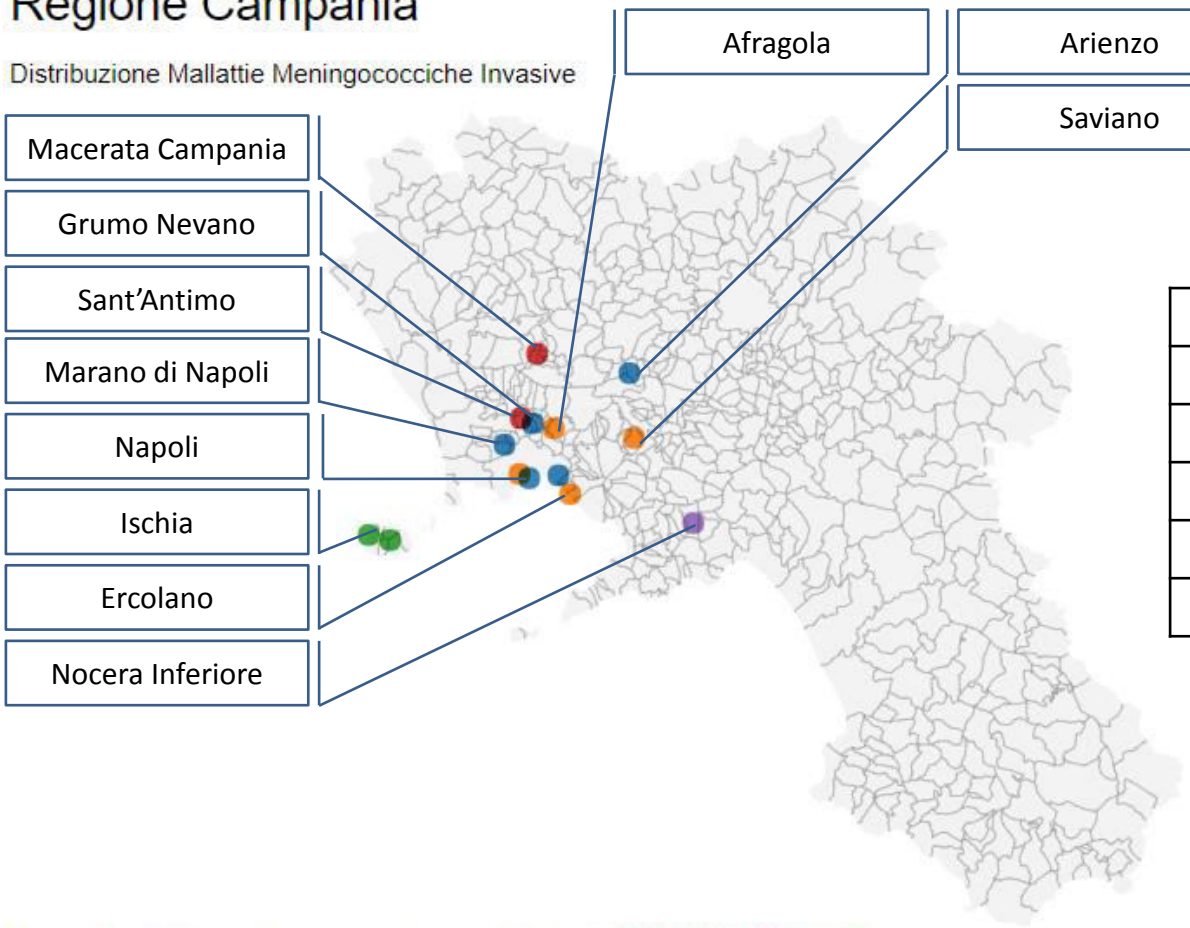
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018*
Neisseria meningitidis	5	8	9	12	18 (1+)	10	13 (1+)	14 (1+)	29 (1+)	18 (1+)	*15 (6+)*
Streptococcus pneumoniae	14	9	14	17 (4+)	20 (6+)	29 (1+)	27 (5+)	23 (6+)	25 (6+)	33 (10+)	*16 (3+)*
Non noto	28	23	39	14	15	13	11	15	9	11	--
Altri streptococchi	--	1	3	1	4	3	2	2	1	3	*1*
Haemophilus	--	--	2	1	--	2	--	2	3	4	--
Stafilococchi	--	--	3	1	4	1	--	3	--	--	--
Listeria	--	--	--	3	5	5	1	1	2	4	*2*
Altri batteri	--	--	--	1	1	2	3	2	5	5	--
Totale	**47**	**41**	**70**	**50**	**67**	**65**	**57**	**62**	**74**	**78**	***34***

Meningococchi Campania 2018

- **1)** 5 anni**, deceduto** sierotipo C St type 11, P1.5,-1.,10-8:F3-6,
- **2)** 23 anni, vivo C, cc10127
- **3)** 1 anno, **deceduta** W, st 11, P1.5, 2:F1-1
- **4**, 64 anni, **deceduta**, Y, st 23,P1.5-2, 10-2:F2-F3
- **5)** 74 anni**,** viva, Y, st 23,
- **6)**, 21 anni, viva, amputata, C, St type 11, P1.5,-1.,10-8:F3-6
- **7)** 28 anni, **deceduto**, W, st 11, P1.5, 2:F1-1
- 8) 5 anni , B vivo
- 9) 8 Mesi, **deceduta**, C, St 11, P1.5,-1.,10-8:F3-6
- 10) 18 mesi sopravvissuto, sierogruppo B,, vivo.
- 11) 16 anni, **deceduto**, sierogruppo C, St 11, P1.5,-1.,10-8:F3-6,
- 12) 51 anni, sopravvissuta, Siero Y.
- 13) 62 anni, sopravvissuta, siero Y.

Regione Campania

Distribuzione Mallattie Meningococciche Invasive



Colour	Serogroups
●	B
●	C
●	Y
●	W
●	Non groupable

Map: Dott. Carlo Tascini • Source: Ospedale Cotugno • Created with Datawrapper

Modello Ischia

- Chemioprofilassi dei contatti secondo protocollo standard
- Azioni secondarie
- Sensibilizzazione della popolazione
- Screening di tutti i familiari e contatti stretti: tutti negativi a livello faringeo per *N. meningitidis*
- Ring Vaccination
- 7.000 persone vaccinate ad Ischia

Assemblea con la popolazione a Serrara Fontana



Azioni di contrasto

- Ring vaccination dei contatti stretti e dei familiari dei soggetti con ST 11
- Rinforzo della campagna di vaccinazione per meningococco
- Apertura dell'ambulatorio vaccinazioni presso Ospedale Cotugno?

Azioni di Contrasto

- Protocollo diagnostico terapeutico in fase di adozione
- Diffusione del protocollo con interventi educazionali atti a sensibilizzare i medici di PS, medici di medicina generale e pediatri di libera scelta sulla diagnosi clinica, sulla terapia precoce e sulla diagnosi microbiologica
- Protocollo sperimentale di studio per lo screening dei contatti stretti dei casi di malattia invasiva meningococcica (in approvazione presso Comitato etico Az. Osp dei Colli di Napoli): utile per stabilire la circolazione dei ceppi clonali

Terapia empirica e mirata

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions associated with causing immunocompromise.

TABLE 4.2. Specific antibiotic in-hospital treatment for community-acquired bacterial meningitis[a]

Microorganism	Standard treatment	Alternatives	Duration
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	7 days
Penicillin resistant (MIC ≥0.1 μg/mL)	Ceftriaxone or cefotaxime	Cefipime, meropenem, ciprofloxacin or chloramphenicol	7 days

Cortisone

Grade A	Empiric treatment with dexamethasone is strongly recommended for all adults (10 mg qid for 4 days) and children (0.15 mg/kg qid for 4 days) with acute bacterial meningitis in the setting of high-income countries.
Grade A	Treatment with dexamethasone is strongly recommended to be initiated with the first dose of antibiotic treatment.
Grade C	If intravenous antibiotic treatment has already been started, dexamethasone can still be administered up to 4 hours after start of the first dose of intravenous antibiotics.
Grade B	It is recommended to stop dexamethasone if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H. influenzae* or *S. pneumoniae,* although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium.

Adjunctive dexamethasone in adults with meningococcal meningitis

Sebastiaan G.B. Heckenberg, MD*
Matthijs C. Brouwer, MD, PhD*
Arie van der Ende, PhD
Diederik van de Beek, MD, PhD

Dexamethasone, 10 mg IV, given every 6 hours for 4 days was started before or with the first dose of parenteral antibiotics in 78 of 96 episodes (81%). In 6 patients (6%), dexamethasone was discontinued after cultures grew meningococci. Dexamethasone was prescribed in 35 of 39 patients (90%) with a rash on admission. Adjunctive dexamethasone was administered in 43 episodes (17%) in the 1998–2002 cohort. Twelve of these patients were included in the European dexamethasone in adulthood bacterial meningitis study and received dexamethasone 10 mg IV, given every 6 hours for 4 days, started before or with first dose of parenteral antibiotics; dexamethasone was initiated after clinical deterioration in all other episodes.[4,13]

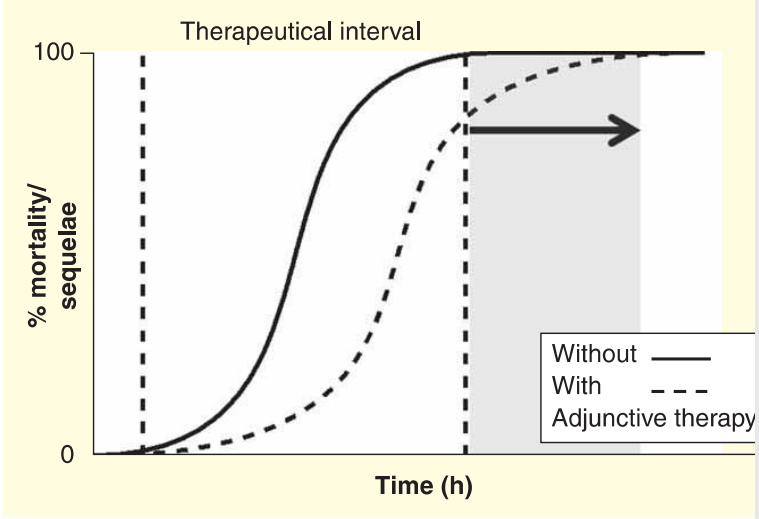


Figure 2. Relation of the interval between entry of bacteria into the CNS and start of antibiotic treatment versus mortality. Our experience in experimental mice suggests that this relation can be described by a sigmoid curve with a steep slope close to the interval where 50% mortality occurs (black solid line). Adjuvant therapies or an improvement of antibiotic therapy (e.g., non-bacteriolytic bactericidal antibiotics) can only be effective in a narrow window (the therapeutic interval) by shifting the sigmoid curve to the right without or with alteration of its slope (black broken line). The black arrow and the grey area indicate the broadening of the therapeutic window by an improvement of therapy. When antibiotic therapy is started very early, all patients will survive. When antibiotic treatment is started after the point of no return, the infected organism will die irrespective of the therapy chosen. The relations of the interval between entry of bacteria into the CNS and start of antibiotic treatment versus other outcome parameters (e.g., long-term neurological sequelae) probably also follow sigmoid curves. The slopes, however, are not necessarily identical. Here, effective adjuvant therapies or an improved antibiotic therapy also shift the curve to the right.

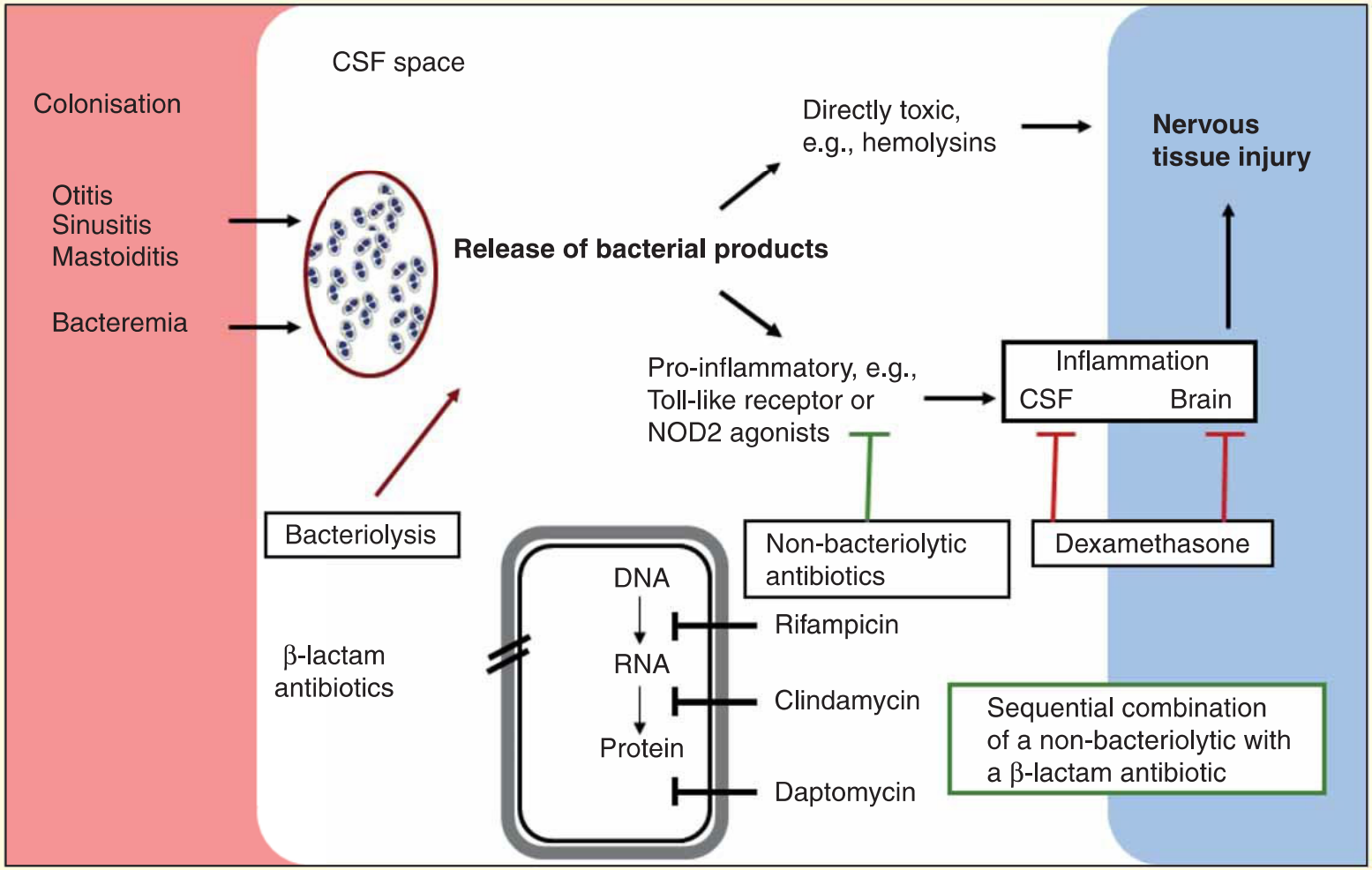
Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

Bacterial meningitis: an update of new treatment options

Roland Nau, Marija Djukic, Annette Spreer, Sandra Ribes & Helmut Eiffert

Quick and dirty versus killing bacteria softly



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ANTI-ENDOTOXIN THERAPY FOR FULMINANT MENINGOCOCCAL SEPTICAEMIA – PILOT STUDY

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[a]*Senior Registrar, Paediatrics, Institute of Child Health,* [b]*Dept. of Medical Microbiology,* [c]*Consultant Paediatrician,* [d]*Institute of Child Health, all at Royal Liverpool Childrens' Hospital (Alder Hey), England*

(Received August 1, 1990)

Terapia colistina 2 mg/Kg +
IGAM 5ml/Kg ogni 12 ore, (0,25mg/Kg/die), per 2 gg
Sopravvivenza 8/11 (72%) contro 6/21 (28%) controli storici

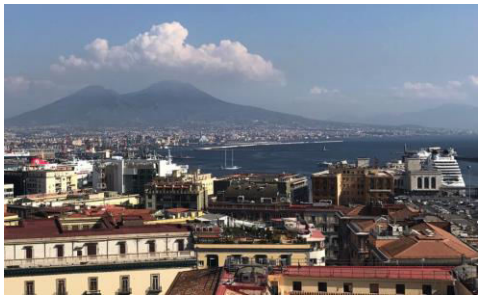


Intensive Care Med
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LETTER

Potential role of IgM-enriched immunoglobulin as adjuvant treatment for invasive meningococcal disease

Carlo Tascini[1], Fiorentino Fraganza[2], Francesca Salani[3], Emanuela Sozio[4], Marco Rossi[1], Francesco Sbrana[5], Novella Carannante[1], Maria Daniela Chiesa[2], Andrea Ripoli[5], Giacomo Bertolino[6], Massimo Di Pietro[7], Alessandro Bartoloni[8,9] and Francesco Menichetti[3*], on behalf of GISA/SIMIT Meningitis Study Group



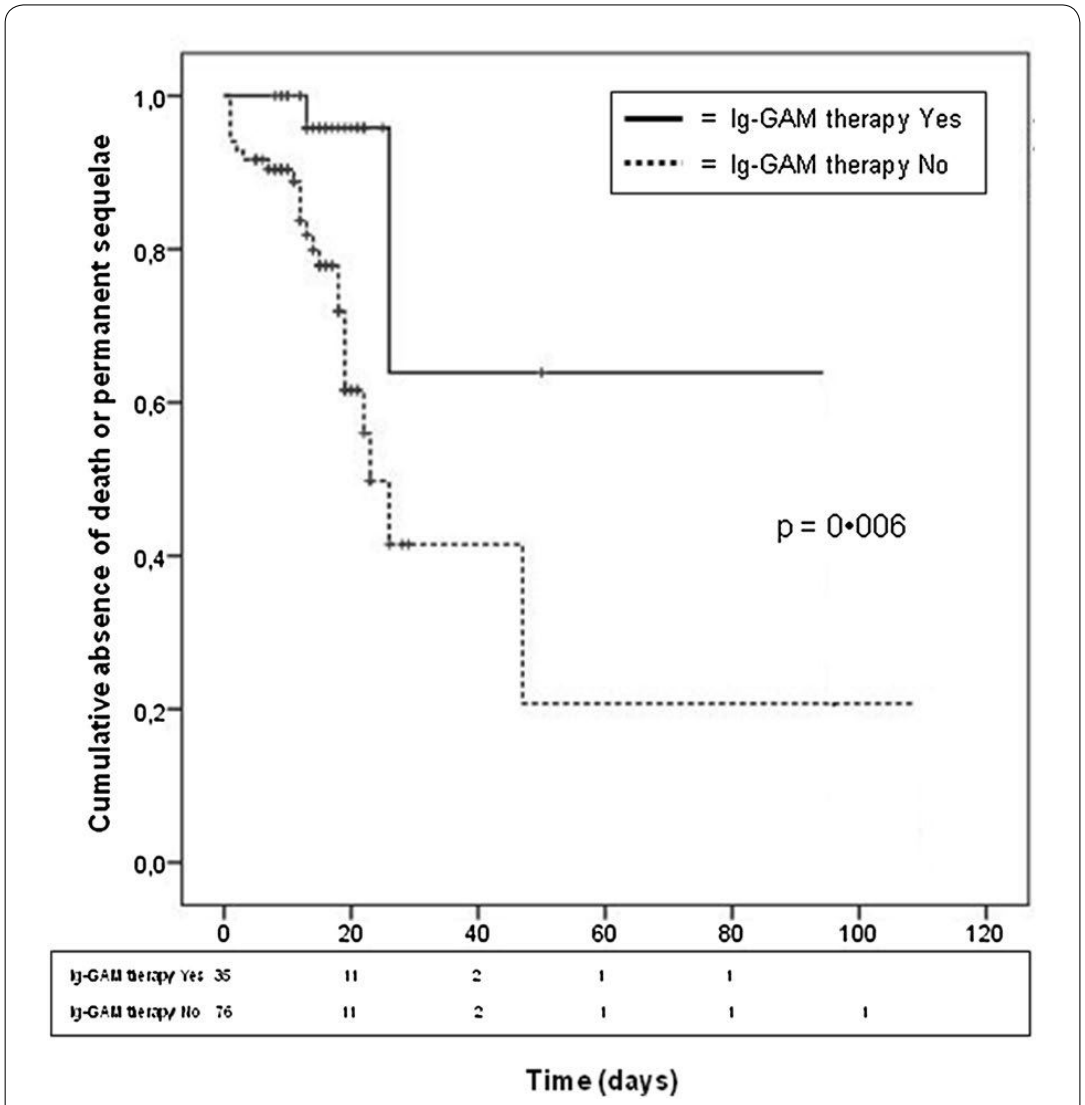
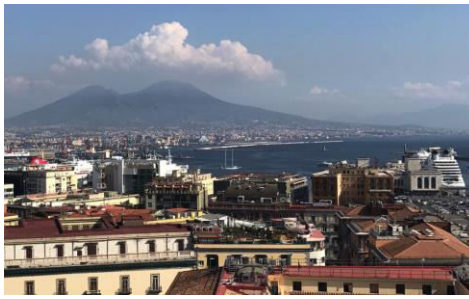
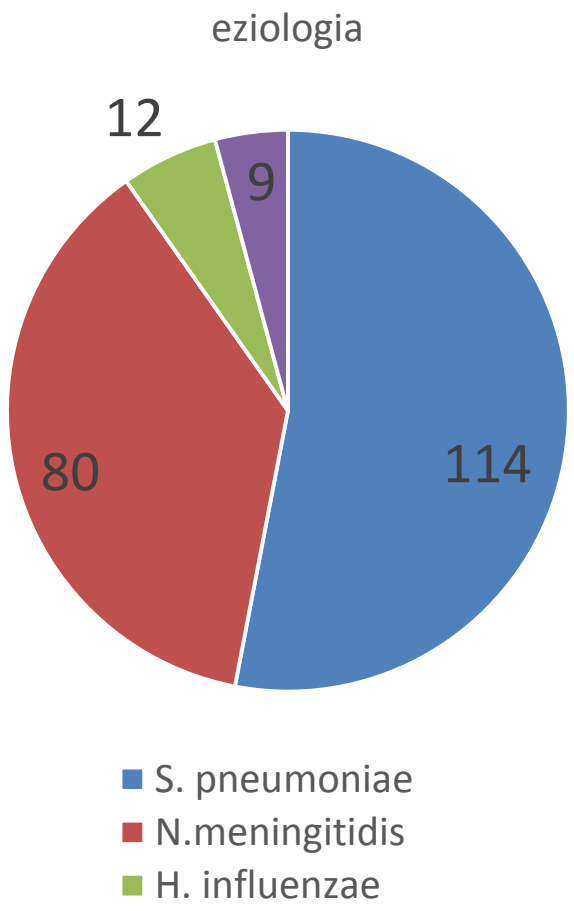


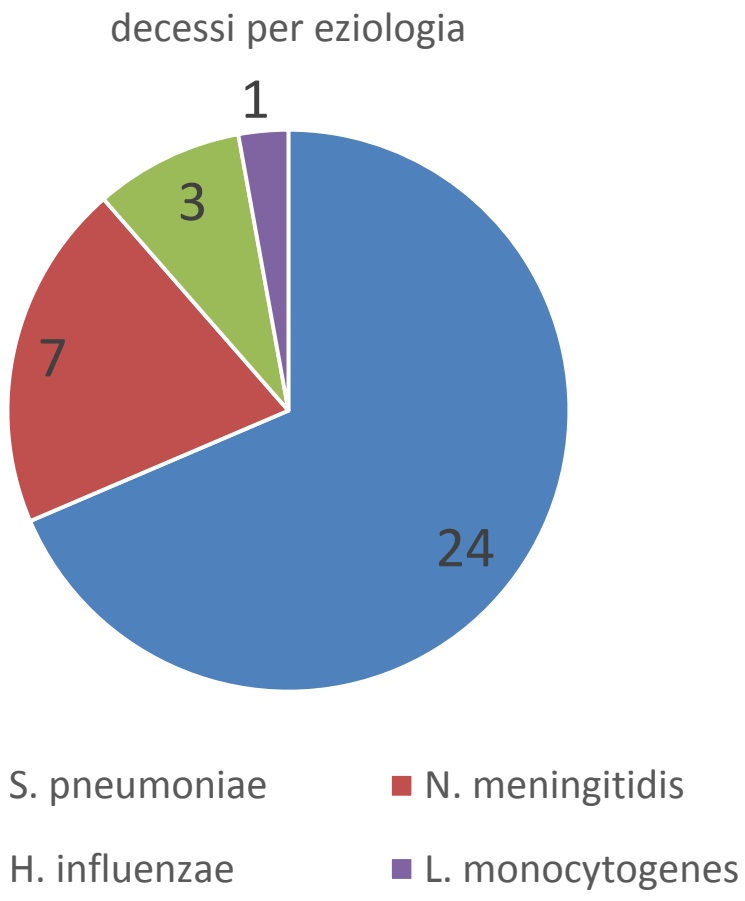
Fig. 1 Kaplan–Meier analysis of aggregated data on death and permanent sequelae in patients treated or not with Ig-GAM



Epidemiologia Cotugno

Da gennaio 2014 ad aprile 2018 sono stati arruolati 215 pazienti con MIB





PIRO score

	Criteri	Punti
Predisposizione	Neoplasia non controllata	1
	Colonizzazione MDR e/o colonizzazione Candida	1
	Neutropenia; immunosoppressione	1
	Allo-HSCT	1
	Splenectomizzato	1
Insulto	Fascite necrotizzante; malattia invasiva meningococcica, pneumococcica,	5
	S pyogenes, CA-MRSA	2
	MDR (accertato) oppure infezione nosocomiale	2
	Peritonite secondaria/terziaria	
Risposta	Conta linfocitaria < 600/ul	2
	IgM < 60 mg/dl	2
	PCT > 10 mg/l e PCR > 20 mg/dl	1
	PCT > 100 ng/l oppure Endotossina >0,6 oppure IL-6 >1000 pg/ml oppure	2
	adrenomedullina >4 nm/l oppure presepsina >1400 ng/l	
	CID score	
Organo	Shock settico	3
	Sepsi con > 2 insufficienza d'organo	2
	Infezione senza sepsi	1

≤ 5 utilizzare vaso per caso

> 5-10 utilizzo suggerito

> 10 utilizzo fortemente suggerito

N. meningitidis e IGAM

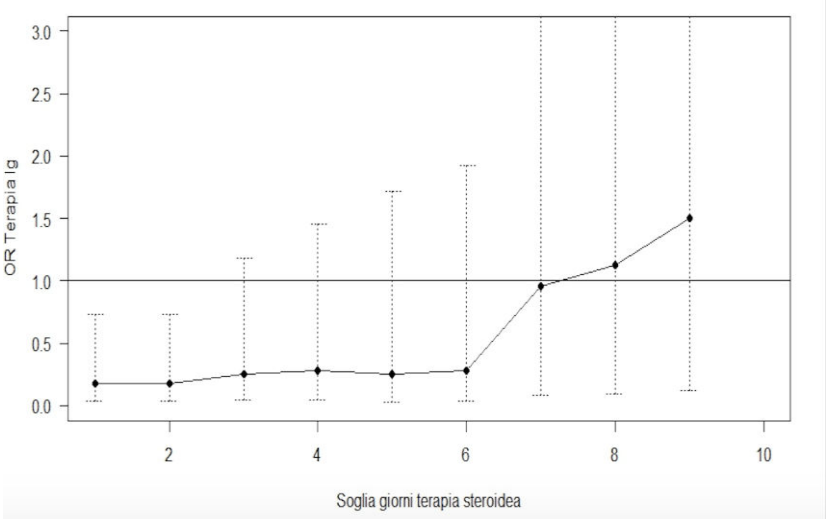
Outcome composito

Punteggio PIRO	OR	OR 2.5° percentile	OR 97.5° percentile	P
5	0.1505	0.0357	0.5330	**0.0052**
6	0.1379	0.0324	0.4936	**0.0037**
7	0.1286	0.0290	0.4813	**0.0036**
8	0.2222	0.0444	0.9939	**0.0536**
9	0.2564	0.0458	1.2633	0.1022
10	0.15	0.0141	1.1494	0.0812

N. meningitidis e IGAM+desametasone

outcome composito

	OR	OR 2.5° percentile	OR 97.5° percentile	p
Giorno 1	0.1765	0.0341	0.7312	0.0224
Giorno 2	0.1765	0.0341	0.7312	0.0224
Giorno 3	0.2545	0.0684	1.1779	0.0860
Giorno 4	0.2813	0.490	1.4513	0.1289
Giorno 5	0.2529	0.0301	1.7185	0.1603
Giorno 6	0.2821	0.0334	1.9245	0.1971
Giorno 7	0.9524	0.0814	21.9270	0.9697
Giorno 8	1.1250	0.0943	26.2102	0.9275
Giorno 9	1.5000	0.1240	35.2291	0.7554



- La diagnosi clinica di malattia invasiva da batteri capsulati può essere molto sfumata: al minimo sospetto procedere con la PL
- La porpora fulminante deve essere riconosciuta: emocolture (test molecolare su sangue, campione per ISS)
- Desametasone (IGAM?)
- Rifampicina
- Ceftriaxone
- IGAM

progetto

MENINGITALY

Meningiti batteriche e malattie invasive ad esse correlate: caratteristiche epidemiologiche, cliniche ed approcci terapeutici

Studio osservazionale, prospettico, multicentrico

Raccolta di dati clinici, epidemiologici, microbiologici e terapeutici mediante scheda informatizzata (Google Moduli) di casi di meningite batterica (non tubercolare) e malattie invasive ad esse correlate

Obiettivo: creazione di un registro nazionale prospettico

Centri partecipanti al momento: 1) Prima Divisione, Malattie Infettive ad indirizzo neurologico, Osp. Cotugno, AORN dei Colli, Napoli; 2) Clinica delle Malattie Infettive, AOU di Perugia; 3) Clinica delle Malattie Infettive, AO di Terni

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