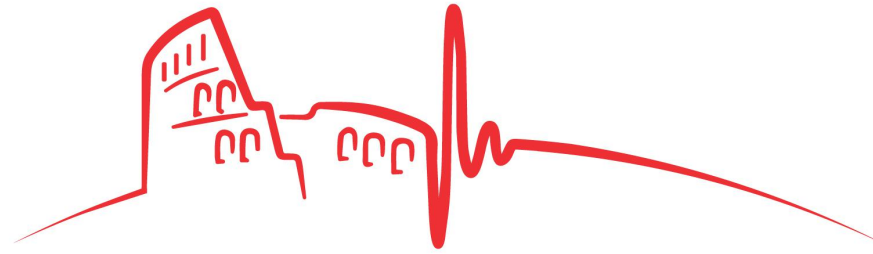


25 Maggio 2018



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**Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella
Malattia Meningococcica Invasiva**

Sessione: Workshop infezioni e Trauma

25 Maggio 2018



Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

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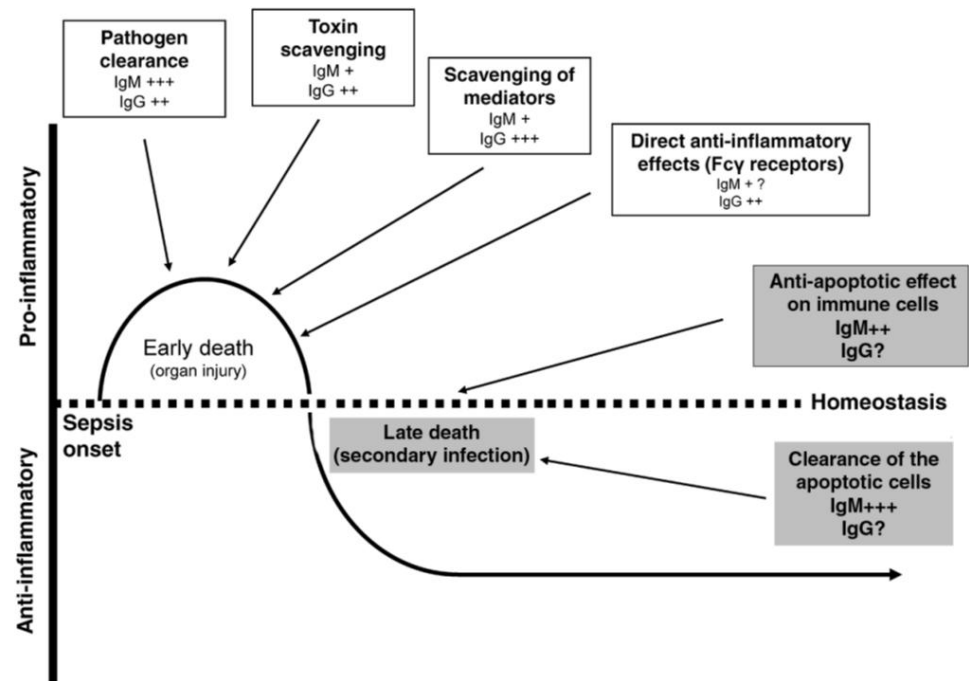
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Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

E. Sozio

Le immunoglobuline IgM possono:

- ✓ migliorare l'opsonizzazione;
- ✓ prevenire l'attivazione indiretta del complemento;
- ✓ proteggere contro la liberazione endotossina indotta dalla terapia antibiotica;
- ✓ neutralizzare sia l'endotossina, che un'ampia varietà di superantigeni di origine batterica.



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Busani S, et al. "Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness". *Minerva anesthesiol* (2016); 82: 559-572.



Il ruolo potenziale delle Ig-GAM come terapia adiuvante

E. Sozio

Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock (Review)

Alejandria MM, Lansang MAD, Dans LF, Mantaring III JB



- Cochrane Review, 2013
Ig ev come tp adiuvante in sepsi e shock settico
- Metanalisi del 1999 e successivi update nel 2002 e 2008, RCTs di comparazione Ig ev (mono polyclonali) con placebo o nessun intervento
- 43 studi (di 88 potenzialmente eleggibili)
- Conclusioni non esaustive

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 9

<http://www.thecochranelibrary.com>



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Il ruolo potenziale delle Ig-GAM come terapia adiuvante

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Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock*

K. Georg Kreymann, MD; Geraldine de Heer, MD; Axel Nierhaus, MD; Stefan Kluge, MD

Objective: There is ongoing debate about the efficacy of polyvalent immunoglobulins as adjunctive therapy for sepsis or septic shock. Two meta-analyses by the Cochrane collaboration calculated a significant reduction in mortality. However, data of the largest study were missing in one, and a subset of four high-quality studies failed to show an effect in the other. To broaden the database, we performed a meta-analysis of all randomized controlled studies published so far.

Data Source: MEDLINE, EMBASE, Cochrane Library of randomized trials, and personal files.

Study Selection: Meta-analysis of all published randomized controlled studies published on polyvalent immunoglobulins (Ig) for treatment of sepsis or septic shock in adults, children, or neonates.

Data Extraction: Twenty-seven trials with a total of 22,222 patients fulfilled the inclusion criteria.

Data Synthesis: As the immunologic state of neonates is different than that of adults or older children, data were evaluated separately for each group. Fifteen trials on 1,492 adults could be

included. The pooled effect on mortality was a relative risk of death (RR) of 0.79 (95% confidence interval [CI] 0.69–0.90, $p \leq .0003$). There was a strong trend in favor of an immunoglobulin preparation enriched with IgA and IgM (IgGAM) (RR = 0.66, 95% CI 0.51–0.84, $p \leq .0009$) compared with preparations containing only IgG (RR = 0.85, 95% CI 0.73–0.99, $p \leq .04$). In 12 trials on 710 neonates, the pooled effect on mortality was 0.56 (95% CI 0.42–0.74, $p \leq .0001$). There was also a positive although less pronounced trend favoring the effect of IgGAM (RR = 0.50, 95% CI 0.34–0.73, $p \leq .0003$) compared with IgG (RR = 0.63, 95% CI 0.42–0.96, $p \leq .03$). A sensitivity analysis selecting eight trials in adults and ten in neonates of highest methodological quality confirmed these results.

Conclusions: Polyvalent immunoglobulins exert a significant effect on mortality in sepsis and septic shock, with a trend in favor of IgGAM. (Crit Care Med 2007; 35:2677–2685)

Keywords: immunoglobulins; immunoglobulin G; immunoglobulin M; randomized controlled trial; systematic review; meta-analysis; sepsis; septic shock; humans



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Il ruolo potenziale delle Ig-GAM come terapia adiuvante

E. Sozio

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ORIGINAL

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Massimo Girardis

Early therapy with IgM-enriched polyclonal immunoglobulin in patients with septic shock

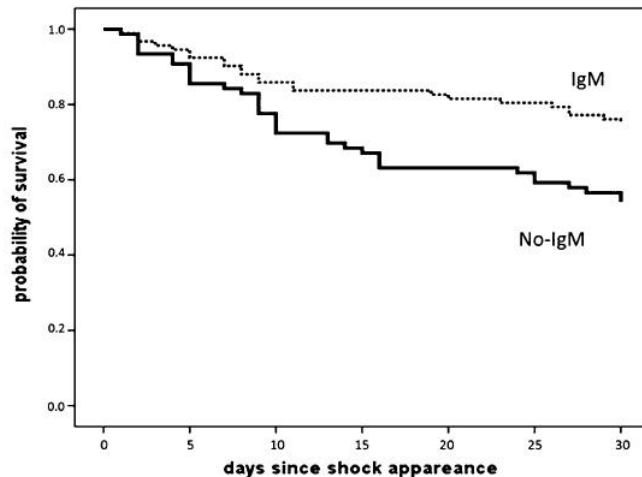


Fig. 1 Probability of cumulative 30-day survival in patients with and without polyclonal IgM therapy

Purpose: To determine if there was an association between adjunctive therapy with IgM-enriched immunoglobulin (IgM) and the 30-day mortality rate in patients with septic shock. **Methods:** In 2008 we introduced IgM as a possible adjunctive therapy to be provided within 24 h after shock onset in the management protocol for patients with septic shock. In this retrospective study we included the adult patients suitable for IgM therapy admitted to our ICU from January 2008 to December 2011. An unadjusted comparison between patients who did or did not receive IgM therapy, a multivariate logistic model adjusted for confounders and propensity score-based matching were used to evaluate the association between early IgM treatment and mortality. **Results:** One hundred and sixty-eight patients were included in the study. Of these, 92 (54.8 %) received IgM therapy. Patients who did or did not receive IgM were similar with regards to infection characteristics, severity scores and sepsis treatment bundle compliance.

Patients who received IgM were more likely to have blood cultures before antibiotics and to attain a plateau inspiratory pressure less than 30 cmH₂O ($p < 0.05$). The 30-day mortality rate was reduced by 21.1 % ($p < 0.05$) in the group that received IgM compared to the group that did not. The multivariate adjusted regression model (OR 0.17; CI 95 % 0.06–0.49; $p = 0.001$) and the propensity score-based analysis (OR 0.35; CI 95 % 0.14–0.85; $p = 0.021$) confirmed that IgM therapy was associated with reduced mortality 30 days after the onset of septic shock. **Conclusions:** Our experience indicates that early adjunctive treatment with IgM may be associated with a survival benefit in patients with septic shock. However, additional studies are needed to better evaluate the role of IgM therapy in the early phases of septic shock.

Keywords Sepsis · Immunoglobulin · Shock · Sepsis bundles · Intensive care



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Il ruolo potenziale delle Ig-GAM come terapia adiuvante

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Relationship
between the timing
of administration of
IgM and IgA
enriched IG in
sepsis and septic
shock: a
retrospective
analysis on the
Outcome

Berlot G et al J Crit Care
2012;27(2):167-71

Table 1 Characteristics of study sample

	Nonsurvivors (n = 42)	Discharged alive (n = 87)
Sex		
Male	27 (20.9%)	54 (41.9%)
Female	15 (11.6%)	33 (25.6%)
Diagnosis at admission		
Urgent surgery	12 (9.3%)	35 (27.1%)
Elective surgery	12 (9.3%)	15 (11.6%)
Medical condition	14 (10.9%)	34 (26.4%)
Trauma	4 (3.1%)	3 (2.3%)
Age (y)	66 (53-74)	64 (52-74)
SAPS II	56 (44-65)	51 (42-63)
Delay for antibiotics (h)	1 (0-2)	1 (0-3)
Delay for immunoglobulins (h)	63 (10-239)	23 (10-64)
Length of stay (d)	13 (4-19)	12 (7-26)
Onset of septic shock		
In general ward	26 (20.2%)	52 (40.3%)
In ICU	16 (12.4%)	35 (27.1%)

Values are absolute frequencies (relative frequencies) or medians (interquartile ranges).



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Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

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Terapia Antibiotica e Terapia Adiuvante nella Malattia Meningococcica Invasiva: Studio Retrospektivo dei Casi Toscani e Campani.

SCOPO: Valutare il potenziale ruolo della terapia adiuvante con Immunoglobuline arricchite da IgM (Ig-GAM) nel ridurre la mortalità e l'insorgenza di sequele permanenti, nei pazienti con MMI.

Studio retrospettivo e multicentrico = 111 casi di MMI: Toscana (53 casi) e Napoli (58 casi), Ottobre 2013 a Dicembre 2016.

- Tutti i pazienti sono stati trattati con terapia antibiotica come da linee guida internazionali; di questi, 35 hanno ricevuto terapia adiuvante con Ig-GAM vs 76 che non hanno ricevuto tale trattamento.
- Analisi descrittiva dei casi e analisi delle differenze dei casi avvenuti nelle due regioni italiane,
- Valutazione dell'impatto della terapia con Ig-GAM sulla mortalità o sulle sequele permanenti.



Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

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Terapie adiuvanti= ridurre l'abnorme risposta infiammatoria ed immunitaria innescata da componenti batterici

meningococco (LPS e peptidoglicano):
up-regulation delle citochine proinfiammatorie
down-regulation delle proteine anti-infiammatorie

Il forte potere anti-infiammatorio dei corticosteroidi, è il razionale dell'uso del desametasone anche per le meningiti meningococciche (ma non nelle LG)

- In caso di sospetta meningite batterica -> Le linee Guida IDSA e ESCMID raccomandavano l'uso di desametasone:
 - 10 mg ogni 6 ore per i primi 4 giorni negli adulti
 - 0,15 mg/kg ogni 6 ore per 4 giorni nei bambini
- **Desametasone** -> NNT = 1:10 in caso di meningite acuta batterica, e di 1:4 per la meningite causata da *S. pneumoniae*.
- Nonostante non sia nelle LG la terapia adiuvante con desametasone è ampiamente utilizzata nella meningite meningococcica
- **Ruolo potenziale di associazione con rifampicina**

Bretonnière C, et al. "Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study". *Critical Care* 19, 1 (2015), 1[9].

Uppal L, et al. "Role of Rifampin in Reducing Inflammation and Neuronal Damage in Childhood Bacterial Meningitis: A Pilot Randomized Controlled Trial". *Pediatr Infect Dis J.* (2016).



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Van de Beek D, et al. "ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis". *Clin Microbiol Infect.* (2016);22 Suppl 3:S37-62.

Tunkel AR, et al. "Practice guidelines for the management of bacterial meningitis". *Clin Infect Dis* (2004);39:1267.

Brouwer MC, et al. "Corticosteroids for acute bacterial meningitis". *Cochrane Database of Systematic Reviews* (2015); 9:CD004405.



Terapia Antibiotica e Terapia Adiuvante nella Malattia Meningococcica Invasiva: Studio Retrospettivo dei Casi Toscani e Campani

Variabili	Popolazione globale (n = 111)	Regione Campania (n = 58)	Regione Toscana (n = 53)	p
Sierogruppo C	61 (55%)	9 (15.52%)	52 (98%)	<0.001
Forma setticemica	40 (36%)	10 (17.2%)	30 (56.6%)	<0.001
Meningite	20 (18.1%)	15 (25.86%)	5 (9.4%)	<0.05
Setticemia+Meningite	54 (48.6%)	34 (58.6%)	20 (37.7%)	<0.05
Terapia con Ig-GAM	35 (31.5%)	26 (44.83%)	9 (16.9%)	<0.05
Terapia con Rifampicina	39 (35%)	38 (65.52%)	1 (1.8%)	<0.001
Ab ≠ da ceftriaxone	72 (64.8%)	46 (79.31%)	26 (49%)	<0.05
Petecchie	80 (72%)	32 (55.1%)	48 (90.5%)	<0.05
MOF	40 (36%)	8 (13.8%)	32 (60.3%)	<0.05
Sepsi	50 (45%)	34 (58.6%)	16 (30.2%)	<0.05
Porpora fulminante	26 (23.42%)	6 (10.34%)	20 (37.7%)	<0.05
Decesso	13 (11.7%)	3 (5.17%)	13 (24.5%)	<0.05
Decesso o reliquati	30 (27%)	9 (15.52%)	21 (39.6%)	<0.05
Età (anni)	27 [15 - 49]	19 [2 - 42]	30 [23 - 53]	<0.001

Variabili non significative nel confronto:

- Sesso Maschile (56.7%)
- Terapia empirica con ceftriaxone (87.38%)
- Terapia con corticosteroidi (81.9%)
- CID (31.1%)
- Shock settico (23.42%)
- SOFA Score 4 [2-7]
- ΔT esordio-Tp empirica: 1 giorno [1-2]
- ΔT esordio-Tp mirata: 0 giorni [0-1]
- Ricovero in UTI: 63%
- Comorbidità (34.3%)
- Fattori di rischio (37.83%)

Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

E. Sozio

Intensive Care Med

DOI 10.1007/s00134-017-4957-z

LETTER



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

Carlo Tascini¹, Fiorentino Fraganza², Francesca Salani³, Emanuela Sozio⁴, Marco Rossi¹, Francesco Sbrana⁵, Novella Carannante¹, Maria Daniela Chiesa², Andrea Ripoli⁵, Giacomo Bertolino⁶, Massimo Di Pietro⁷, Alessandro Bartoloni^{8,9} and Francesco Menichetti^{3*}, on behalf of GISA/SIMIT Meningitis Study Group



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Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

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Supplementary Table 2: Univariate logistic regression for death and permanent sequelae prediction

Variables	OR [95% CI]	p
Age (years)	1.027 [1.005 – 1.048]	0.014
Male gender	0.857 [0.354 – 2.073]	0.732
Tuscany region	2.571 [1.029 – 6.442]	0.043
<i>N. meningitidis</i> , serogroup C	3.357 [1.277 – 8.823]	0.014
SOFA score	1.219 [1.094 – 1.358]	<0.001
• Respiratory SOFA	1.202 [0.906 – 1.594]	0.202
• Kidney SOFA	1.991 [1.231 – 3.220]	0.005
• Neuro SOFA	1.271 [0.896 – 1.803]	0.178
Glasgow Coma Scale	0.929 [0.816 – 1.058]	0.269
Admission in ICU	2.449 [0.893 – 6.715]	0.082
Clinical manifestations of IMD:		
🕒 Meningitis	1.111 [0.361 – 3.417]	0.854
🕒 Meningococemia	3.145 [1.269 – 7.793]	0.013
🕒 Meningitis + Meningococemia	0.184 [0.063 – 0.533]	0.002
🕒 <i>Purpura fulminans</i>	7.500 [2.723 – 20.656]	<0.001
🕒 Severe coagulopathy (DIC)	3.341 [1.343 – 8.309]	0.009
🕒 Septic shock	4.071 [1.545 – 10.731]	0.005
Empirical therapy with Ceftriaxone	0.497 [0.151 – 1.643]	0.252
Other empirical antibiotic therapy	1.639 [0.620 – 4.329]	0.319
Renal replacement therapy	4.952 [1.589 – 15.431]	0.006
Use of steroid therapy	1.125 [0.337 – 3.757]	0.848
Days from clinical onset to empirical therapy	0.753 [0.512 – 1.109]	0.151
Ig-GAM therapy	0.216 [0.060 – 0.777]	0.019

Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

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Variables	OR
Age (years)	1.011
Tuscany region	-----
<i>N. meningitidis</i> , serogroup C	-----
SOFA score	1.047
• Kidney SOFA	-----
Admission in ICU	-----
Clinical manifestations of IMD:	
🕒 Meningococemia	-----
🕒 Meningitis + Meningococemia	0.672
🕒 Purpura fulminans	3.160
🕒 Severe coagulopathy (DIC)	1.151
🕒 Septic shock	-----
Renal replacement therapy	1.105
Ig-GAM therapy	0.599

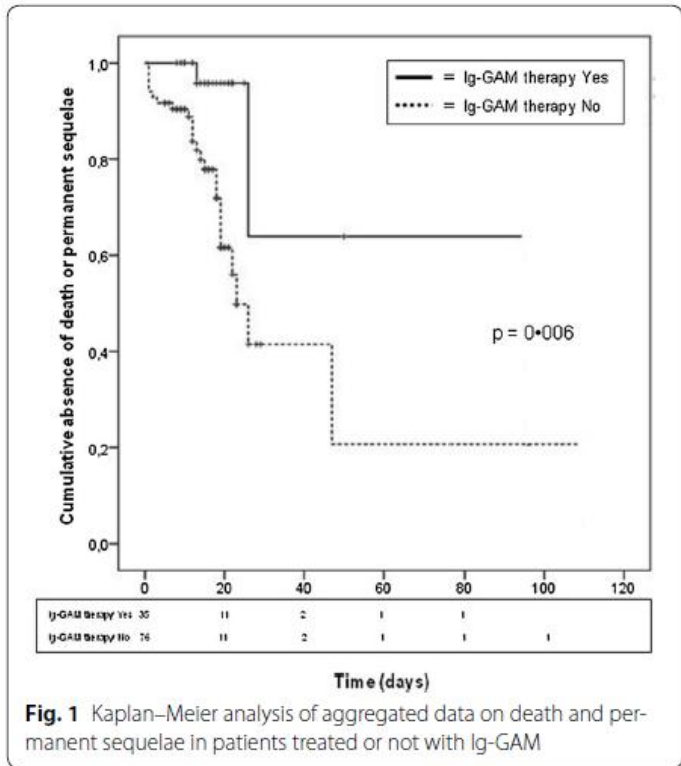
Supplementary Table 3: Multivariate penalized logistic regression for death and permanent disease prediction

Comment: Multivariate penalized logistic regression model, for death or permanent disease prediction, showed that therapy with Ig-GAM reduced (OR=0.599) the probability of death and permanent sequelae, while the presence of purpura fulminans appeared as the strongest risk factor for death (OR=3.160), and a role has been found also for DIC (OR=1.151), renal replacement therapy (OR=1.105), SOFA score (OR=1.047) and advanced age (OR=1.011). A protective role was found for Meningitis in patients with Meningococemia (OR=0.672).



Il ruolo potenziale delle Ig-GAM come terapia adiuvante nella Malattia Meningococcica Invasiva

E. Sozio



Our retrospective analysis suggested an improved combined outcome for patients with IMD treated with Ig-GAM. The study suffers some important limitations: (a) the retrospective nature of the observation and (b) the imbalance between the two groups driven by the fact that the decision of administering Ig-GAM was left to the physician (ICU or ID) evaluating the patient in the emergency room. Furthermore, the registered statistically significant difference between patients treated with Ig-GAM or not was on the aggregated data related to deaths and permanent sequelae.

In conclusion, our experience suggests that Ig-GAM adjuvant therapy might have a favourable impact on the overall outcome in patients with IMD. Prospective, randomized clinical trials are therefore warranted.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4957-z) contains supplementary material, which is available to authorized users.

Grazie per l'attenzione!

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