Biotest

From Nature for Life

Pentaglobin®

Evidence for therapeutic use

Meta-analyses show a significant effect on the mortality of severe sepsis and septic shock

Meta-analysis – an evaluation providing high objectivity

Researchers, physicians, people working in the health care sector and patients have a common interest in reliable and up-to-date information regarding prevention, treatment and rehabilitation of certain diseases.

Meta-analyses help them to obtain a quick overview of the current trial situation in a special field and to decide which procedure or treatment is to favour.

Three good reasons for considering meta-analyses

1. Meta-analyses condense knowledge

Medical knowledge is growing at an amazing pace. As a physician it is virtually impossible to know about every trial. Meta-analyses pool results from different trials thus offering a rapid and qualified insight.

2.Meta-analyses allow comparisons

It is sometimes difficult to relate study results from different trials, especially if, as in the treatment of sepsis, the case numbers are very small. Weaknesses in methodology are also not always spotted at first glance. Meta-analyses provide a balanced view of study results relating to a treatment or a specific treatment method.

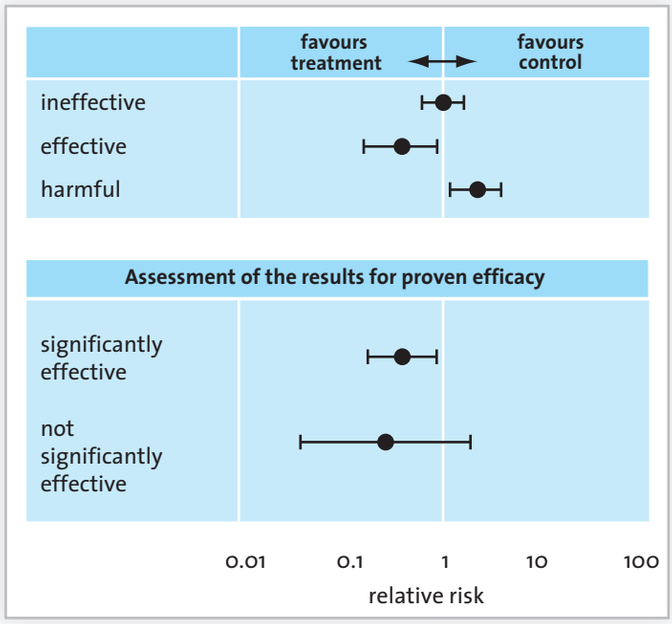
3. Meta-analyses are a reliable source of information

The Cochrane Collaboration, founded in 1993, is a pioneer in the field of meta-analyses. To prevent bias, this non-profit organisation works to strict methodolical standards. Consequently, meta-analyses that conform to these clear standards provide a reliable source of information.

Meta-analysis of an effective drug

Representation of meta-analyses in a so-called Forest Plot permits rapid visual orientation of common trends in analysed studies. If the relative risk is below the value 1, this indicates the efficacy of a drug. Above this value the drug used is ineffective, if not even harmful.

If the efficacy of a drug is proven, the confidence interval (horizontal line) determines the significance of the overall result. If the upper range of the confidence interval is higher than the value 1, efficacy is assessed as follows: The difference found is not significant.



Efficacy of intravenous immunoglobulins confirmed

Since 2002 a total of seven meta-analyses on the use of immunoglobulins in the treatment of sepsis have been published. All these analyses confirm a benefit to sepsis patients of adjunctive intravenous treatment with immunoglobulins.

Publications	Studies included	Number of patients	Relative risk	95 % CI
Alejandria/Cochrane (2002)[1]	11	492	0.64	0.51 – 0.80
Pildal (2004)[2]	21	1,711	0.77	0.68 – 0.88
Neilson (2005)[3]	9	435	0.52	0.39 – 0.68
Norrby-Teglund (2006)[4]	10	645	0.35	0.23 – 0.54
Turgeon (2007)[5]	20	2,621	0.74	0.62 – 0.89
Laupland (2007)[6]	14	1,450	0.66	0.53 – 0.83
Kreymann (2007)[7]	27	2,002	0.71	0.64 – 0.80

The **relative risk (RR)** expresses the factor by which a risk differs in two groups. The **confidence interval (CI)** gives evidence on the precision of how a parameter's position is estimated (for example a mean value). With a 95% CI the true value in 95 of 100 cases is within the calculated interval limits.

Intravenous polyvalent immunoglobulins

Throughout the world the use of standard immunoglobulins (IgG class) is approved for substitution treatment in proven antibody deficiency disorders. In addition polyvalent immunoglobulins are used for the therapeutic modulation of the immune system in a number of autoimmune diseases such as Guillain-Barré syndrome.

Immunoglobulin preparations enriched with IgM and IgA (ivIgGMA) are particularly suitable for treating severe bacterial infections and for substitution of immunoglobulins in patients with immune deficiency.

Pentaglobin® is currently the only immunoglobulin preparation approved for this purpose.

References:

1 Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2002,(1):CD001090.

2 Pildal J, Gøtzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis. 2004,39(1):38-46.

3 Neilson AR, Burchardi H, Schneider H. Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (Pentaglobin) in the treatment of severe sepsis and septic shock. J Crit Care. 2005,20(3):239-249.

4 Norrby-Teglund A, Haque KN, Hammarström L. Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis. J Intern Med. 2006,260(6):509-516.

5 Turgeon AF, Hutton B, Fergusson DA, McIntyre L, Tinmouth AA, Cameron DW, Hébert PC. Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. Ann Intern Med. 2007,146(3):193-203.

6 Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis. Crit Care Med 2007,35(12): 2686-2692.

7 Kreymann KG, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. Crit Care Med. 2007,35(12):2677-2685.

Pentaglobin® is superior to standard IgG therapy

Four meta-analyses have been carried out to analyse the efficacy of adjunctive therapy of sepsis and septic shock with Pentaglobin®. The studies available show that using immunoglobulins significantly reduces the mortality risk of sepsis patients. This influence is much more intensive with ivIgG-MA preparations such as Pentaglobin® than with standard immunoglobulins.

Alejandria MM, Lansang MA, Dans LF et al.

Intravenous immunoglobulin for treating sepsis and septic shock.

Studies included	Number of patients	Relative risk	95 % CI
4	**194**	**0.48**	**0.30 – 0.76**

Cochrane Database Syst Rev 2002; CD001090.

- **Post-hoc sub-analyses according to the type of polyclonal ivIg demonstrated a greater reduction in mortality among patients given IgM-enriched IVIG compared to standard polyclonal IVIG.**

Neilson AR, Burchardi H, Schneider H

Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (Pentaglobin®) in the treatment of severe sepsis and septic shock.

Studies included	Number of patients	Relative risk	95 % CI
9	**435**	**0.52**	**0.39 – 0.68**

J Crit Care. 2005, 20(3): 239-249.

- **Pentaglobin® is a promising adjuvant therapy both clinically and economically for treatment of adults with severe sepsis and septic shock.**

Norrby-Teglund A, Haque KN, Hammarström L

Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis.

Studies included	Number of patients	Relative risk	95 % CI
10	**645**	**0.35**	**0.23 – 0.54**

J Intern Med. 2006,260(6):509-516.

- **The results suggest that patients most likely to benefit from IgM-enriched IVIG therapy are those with Gram-negative septic shock.**

Kreymann KG, de Heer G, Nierhaus A et al.

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

	Studies included	Number of patients	Relative risk	95 % CI
Adults	**8**	**560**	**0.66**	**0.51 – 0.84**
Children	**5**	**352**	**0.5**	**0.34 – 0.73**

Crit Care Med. 2007, 35(12):2677-2685

- **Polyvalent immunoglobulins exert a significant effect on mortality in sepsis and septic shock, with a trend in favour of IgGMA.**

Advantages of IgM in the treatment of severe bacterial infections

The structural benefits of IgM are apparent for the different modes of action: compared with IgG, IgM has a

- 1000 times higher opsonisation activity
- 100 times more potent agglutination strength
- 100 times higher phagocytic activity
- 400 times higher specific complement activation

There is a multiple increase in the scavenging of activated complement factors, the neutralisation of bacterial toxins, especially endotoxin, and the modulation of the systemic cytokine network.

These benefits have a decisive influence on the clinical status of patients. The table shown below illustrates why ivIgGMA preparations are more effective in sepsis than ivIgG preparations: The higher antibody content and the more intensive complement inhibition of the ivIgGMA preparation result particularly in improved efficacy, especially in the initial sepsis phase.

The results of the meta-analyses confirm the improvement of survival under treatment with ivIgGMA compared to ivIgG.

Therapy of severe bacterial infections

	ivIgG	ivIgGMA
Increase of survival (sepsis)		
Cochrane[1]	↑	↑↑
SBITS study[2]	∅	
Increase of survival (in patient subgroups)		
Peritonitis[3]	↑	↑↑
Meningococcal sepsis[4]	↑	↑↑
Sepsis in the newborn and infants[5,6]	↑	↑↑
Improvement in critical-illness polyneuropathy[7]	?	↑ (retrospective)
Improvement in disturbed microcirculation[8]	∅	↑↑
Decline in severity of the illness (Δ-APACHE II score in the first 4 days)		
SBITS study (sepsis)[2]	- 1.2	
ESSICS study (severe SIRS)[9]	- 0.1	
Septic shock with endotoxaemia[10]		- 5.0

References:

1 Alejandria MM et al. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2002, (1):CD001090.
2 Werdan K et al. Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study. Crit Care Med. 2007, 35(12):2693–2701.
3 Rodriguez A et al. Effects of high-dose of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. Shock. 2005, 23(4):298–304.
4 Thompson AP et al. Anti-endotoxin therapy for fulminant meningococcal septicaemia: pilot study. Arch Dis Child. 1989, 64:1217-1218.
5 Haque KN et al. IgM-Enriched intravenous Immunoglobulin Therapy in Neonatal Sepsis. Am J Dis Child. 1988, 142(12):1293-1296.
6 El-Nawawy et al. Intravenous Polyclonal Immunoglobulin Administration to Sepsis Syndrome Patients: A Prospective Study in a Pediatric Intensive Care Unit. J Trop Ped. 2005, 51:271-278.
7 Mohr M et al. Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Int Care Med. 1997, 23:1144-1149.
8 Hoffmann JN et al. Immunoglobulin M-enriched human intravenous immunoglobulins reduce leukocyte-endothelial cell interactions and attenuate microvascular perfusion failure in normotensive endotoxemia. Shock. 2008, 29(1):133-139.
9 Werdan K et al. for the Early Supplemental Severe SIRS Treatment With IVIG in Score-Identified High-Risk Patients After Cardiac Surgery (ESSICS) Study Group. Immunoglobulin G treatment of postcardiac surgery patients with score-identified severe systemic inflammatory response syndrome – The ESSICS study. Crit Care Med 2008, 36(3):716–723.
10 Schedel I et al. Treatment of gram-negative septic shock with an immunoglobulin preparation: a prospective, randomized clinical trial. Crit Care Med 1991, 19(9):1104-1113.

Pentaglobin® reduces the mortality risk in adults, infants and the newborn

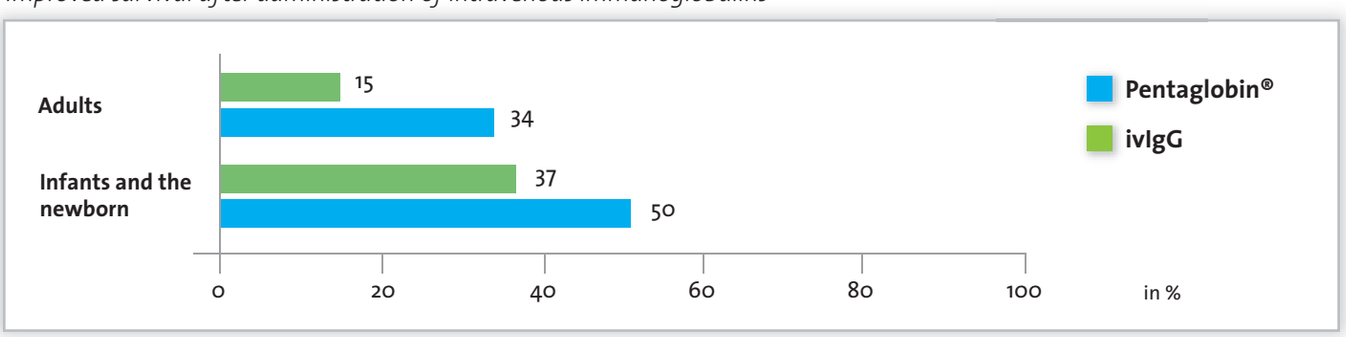
The latest publication on treatment with intravenous polyclonal immunoglobulin by Kreymann et al.[1] recommends the use of IgM- and IgA-enriched immunoglobulins (ivIgGMA) in the adjunctive therapy of sepsis and septic shock. This applies both to treatment of adults and infants and the newborn.

The result analysis for the treatment of adults shows a reduction in the mortality risk by 34 percent. Using ivIgG preparations the mortality risk was reduced by only 15 percent.

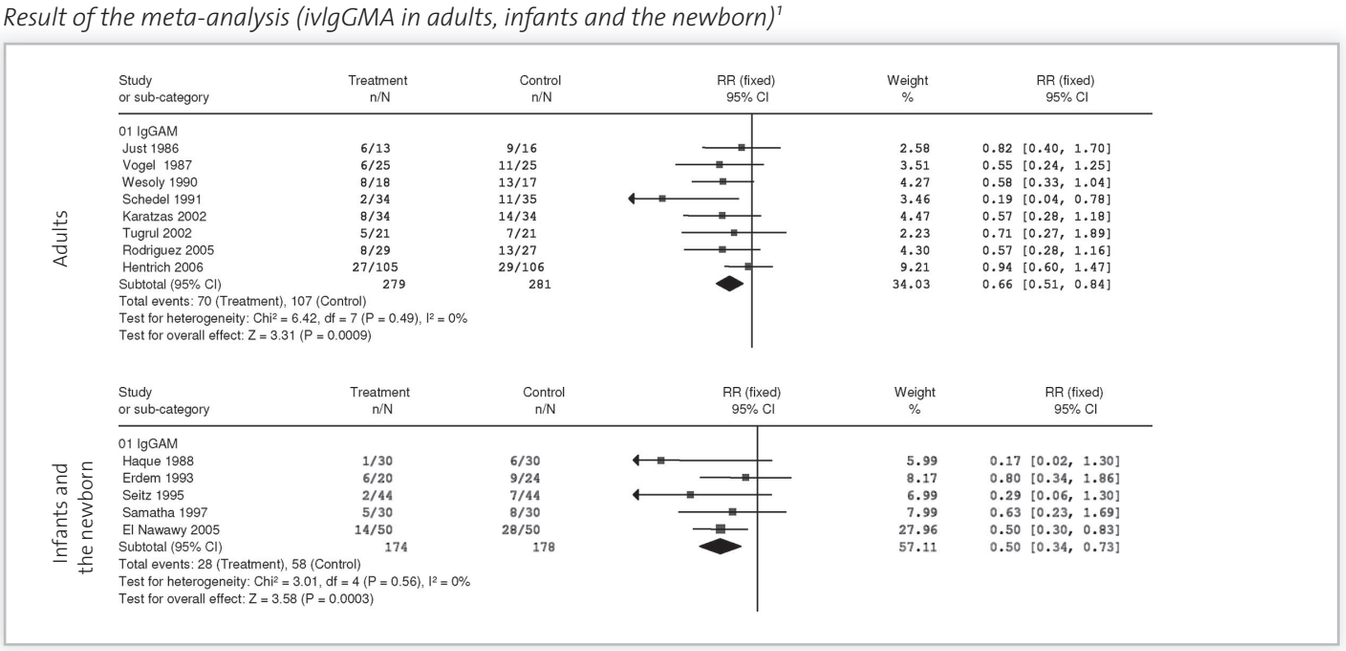
The varying efficacy in the treatment of infants and the newborn can be seen just as clearly. The meta-analysis confirms that the relative mortality risk is reduced under treatment with Pentaglobin® by 50 percent compared with 37 percent under standard intravenous IgG therapy.

The journal "Internist"[2] published the review paper by Kreymann et al. in November 2007 under the title "Immunoglobulin in antibody deficiency syndrome, use in sepsis and other indications?" and reaches the conclusion: The chance of survival in sepsis is improved decisively by the administration of ivIgGMA.

Improved survival after administration of intravenous immunoglobulins



Result of the meta-analysis (ivIgGMA in adults, infants and the newborn)[1]



References:
1 Kreymann KG, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. Crit Care Med. 2007;35(12):2677-2685.
2 Kluge S et al. Immunglobuline bei Antikörpermangelsyndrom – Einsatz auch bei Sepsis und anderen Indikationen? Internist 2007;48(11):2-8.

Experts recommend IgM-enriched immunoglobulin preparation

Two German experts in the field of intravenous immunoglobulin therapy have taken a stand and recommend the use of ivIgGMA (Pentaglobin®) in the renowned journal Critical Care Medicine.

Karl Werdan, MD, Martin-Luther-University, Halle-Wittenberg, Germany

Mirror, mirror on the wall, which is the fairest meta-analysis of all?
Crit Care Med. 2007, 35(12):2852-2854

- **Kreymann et al. tell us: Polyvalent immunoglobulins exert a significant effect on mortality in sepsis and septic shock with a trend in favour of ivIgGMA.**
- **Both types of preparations compared, a superior antibody content and a more intense complement inactivation of ivIgGMA make more differences in the initial stage of sepsis.**
- **3 studies confirm a benefit for a specific patient group (gram-negative septic shock, surgical patients with abdominal sepsis, children with fulminant meningococcal sepsis).**
- **The findings deserve grade C and grade E recommendation for ivIgGMA treatment of the specific sepsis subgroups as indicated.**

Edmund Neugebauer, PhD, University of Witten/Herdecke, Germany

To use or not to use? Polyclonal intravenous immunoglobulins for the treatment of sepsis and septic shock
Crit Care Med. 2007, 35(12):2855-2856

- **Discrepancies between data in previous meta-analyses refer to the non-homogeneity of the collectives investigated. Data were mostly not summarised separately for adults or older children and neonates. Moreover, a differentiation of the preparations comparing IgM-enriched ivIgG preparations with various preparations that contain only ivIgG has not been made.**
- **The well-performed analysis by Dr. Kreymann and colleagues should lead to an upgrade of the current German sepsis guideline recommendation on ivIgGMA use in adults and in children with sepsis or septic shock.**
- **A Grade B recommendation for ivIgGMA use based on the new data presented is appropriate.**

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Evidence for therapeutic use

Meta-analyses show a significant effect on the mortality of severe sepsis and septic shock.

Pentaglobin® combines the active principles for the treatment of bacterial/toxic inflammatory reactions:

- Bactericidal effect due to natural antibacterial antibodies
- Enhancement of the phagocytosis of pathogens
- Neutralisation of bacterial toxins
- Modulation of the systemic cytokine network
- Scavenging of activated complement factors

Composition active ingredients: 1 ml solution contains: Human plasma protein 50 mg of which immunoglobulin at least 95 %, IgM 6 mg, IgA 6 mg, IgG 38 mg. **Other constituents:** Glucose monohydrate (27.5 mg/ml), sodium chloride (78 µmol/ml), water for injections (ad 1 ml) **Therapeutic indications:** Adjuvant therapy of severe bacterial infections additional to antibiotic therapy. Immunoglobulin substitution in immunocompromised patients. **Contraindications:** Intolerance to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA. **Undesirable effects:** Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia and mild back pain may occur occasionally. Rarely immunoglobulins may cause a fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no sensitivity to previous administration. Reversible aseptic meningitis and nephrotoxicity have occurred rarely. In case of adverse reactions either the rate of administration must be reduced or the infusion stopped until symptoms disappear. If severity of reactions persists after discontinuation of the infusion, appropriate treatment is recommended. In case of anaphylactic reaction or shock, treatment should follow the guidelines for shock therapy. Overdosage is possible in overweight and elderly subjects and in those who have impaired renal function (including diabetics at risk for renal failure). In patients with signs of cerebral or cardiac ischaemia, the increase in viscosity caused by an immunoglobulin infusion may be a risk. In these patient groups, 5-6 % solutions should be used and no more than 0.4 g/kg infused daily. Creatinine levels should be measured for 3 days after IVIG infusion. When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature. To reduce the risk of transmission of infective agents, selection of donors and donations by suitable measures is performed, plasma pools are tested, and virus removal/inactivation procedures are included in the production process. For the manufacture of Pentaglobin® only plasma is used which is obtained from healthy donors tested and found negative for HBsAg, for HCV antibodies, for HIV-1/2 antibodies, and showing no pathologically raised ALT-activity. Furthermore, only plasma pools tested and found negative for HBsAg, for HCV antibodies and for HIV-1/2 antibodies are processed. Pentaglobin® is manufactured by cold-ethanol-fractionation. For inactivation of viruses octanoic acid precipitation and treatment with ß-propiolactone are carried out. **Interaction with other medicaments and other forms of interactions:** Pentaglobin® should not be administered concomitantly with calcium gluconate as the suspicion exists that adverse reactions may occur in infants after simultaneous administration. Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. In some cases where large doses are given this impairment period may be as long as 1 year. Passive transmission of antibodies may interfere with some serological tests – e.g. Coombs test, CMV serology etc. **Package sizes:** 10 ml ampoule, 50 ml and 100 ml vial.

The information in this brochure may deviate from the summary of product characteristics valid for your country. Therefore, please refer to your national Pentaglobin® prescribing information.

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