Shock: Injury, Inflammation, and Sepsis: Laboratory and Clinical Approaches

Use of intravenous immunoglobulins in patients with suspected toxin-mediated shock requiring extracorporeal membrane oxygenation --Manuscript Draft--

Manuscript Number:	SHOCK-D-19-00453R4
Full Title:	Use of intravenous immunoglobulins in patients with suspected toxin-mediated shock requiring extracorporeal membrane oxygenation
Short Title:	Use of IVIG in toxin-mediated shock on ECMO
Article Type:	Clinical Aspects (Human Subjects)
Keywords:	septic shock; critical care; toxic shock syndrome; extracorporeal membrane oxygenation; immunoglobulins; Panton-Valentine Leukocidin; Streptococcus pyogenes
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Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	<p>Background: Toxin-producing, Gram-positive bacteria, can lead to severe and refractory septic shock with high attributable mortality. Adjunctive therapies such as intravenous immunoglobulins (IVIG) have been proposed for these patients. However, at presentation the presence of a toxin-producing organism is most often unknown. As IVIG is a potentially valuable but also limited resource, we investigated the use of IVIG in our critically ill patients requiring extracorporeal membrane oxygenation (ECMO).</p> <p>Materials and methods: Retrospective cohort study (April 2016-March 2018) of adult patients with clinically suspected toxin-mediated shock requiring ECMO and who received IVIG in our regional severe respiratory failure (SRF)/ ECMO centre.</p> <p>Results: In 44% (15/34) of the patients, group A Streptococcus or Panton-Valentine Leukocidin producing S. aureus was isolated. IVIG use in these patients was safe. The mortality was 30%, lower than the predicted mortality of >90% based on the SOFA scores.</p> <p>Conclusion : IVIG administration can be considered in a selected group of patients presenting with acute and very severe septic shock.</p>
Response to Reviewers:	<p>Dear Dr Chaudry,</p> <p>We have revised the manuscript title page and reference list to comply with the journal's standards.</p>

Yours sincerely,

Marijke Peetermans,
on behalf of the co-authors

Title

Use of intravenous immunoglobulins in patients with suspected toxin-mediated shock requiring extracorporeal membrane oxygenation

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Conflicts of interest and sources of funding

None to declare.

Running head

Use of IVIG in toxin-mediated shock on ECMO

Word count: abstract: 161 words; manuscript: 1656 words

Abstract

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Materials and methods: Retrospective cohort study (April 2016-March 2018) of adult patients with clinically suspected toxin-mediated shock requiring ECMO and who received IVIG in our regional severe respiratory failure (SRF)/ ECMO centre.

Results: In 44% (15/34) of the patients, group A *Streptococcus* or Panton-Valentine Leukocidin producing *S. aureus* was isolated. IVIG use in these patients was safe. The mortality was 30%, lower than the predicted mortality of >90% based on the SOFA scores.

Conclusion: IVIG administration can be considered in a selected group of patients presenting with acute and very severe septic shock.

Keywords

Septic shock, critical care, toxic shock syndrome, Panton-Valentine Leukocidin, *Streptococcus pyogenes*

Manuscript

Introduction

Intravenous immunoglobulins (IVIG) are advocated for toxin-mediated severe infections. These include streptococcal or staphylococcal toxic shock syndrome (TSS) caused by superantigen production by some strains of *Staphylococcus aureus* or group A *Streptococcus*, as well as necrotizing pneumonia caused by Panton-Valentine Leukocidin (PVL)- positive *S. aureus* [1-5]. TSS is rare with an annual incidence of 1-5 patients per million [6, 7] but it carries a very high mortality of 22-44% [7-9]. Diagnosis is challenging as less than half of patients have positive blood cultures. The clinical phenotype of the disease is broad. Patients can present with pneumonia or without a clear focus on infection [6, 7, 10]. Similarly, PVL production is found in only a small number of *S. aureus* strains [11] but PVL-positive pneumonia has very high mortality rates of >40% [12, 13].

In streptococcal TSS the evidence base supporting the use of IVIG is conflicting. There are two retrospective comparative studies showing a mortality benefit from IVIG [14, 15], but also two negative studies [16, 17]. In staphylococcal toxin-mediated disease, data are limited to in vitro findings [18], case reports and a case series [19]. The theoretical rationale is that IVIG would bind and neutralize superantigens and toxins, hence limiting the downstream inflammatory cascade. Other mechanisms are also proposed, such as direct anti-inflammatory action via Fcγ receptors (4). In other septic shock states not caused by toxin-producing organisms, there remains even more controversy about the potential role of IVIG [20], although the possible anti-inflammatory actions of IVIG via Fcγ receptors, and its effect in opsonization to enhance bacterial clearance, explain the scientific interest for IVIG use in very severe septic shock.

1 The bedside clinician is faced with the dilemma that the availability of IVIG is limited
2 and the diagnosis of toxin-mediated shock challenging. In the USA, the use of IVIG for toxin-
3 mediated sepsis is off-label. In the UK, the Department of Health issued clinical guidelines
4 for IVIG use [21] coupled to a demand management plan. Use of IVIG in severe invasive
5 group A streptococcal disease, staphylococcal toxic shock syndrome and necrotizing PVL-
6 associated staphylococcal sepsis are considered “blue” (medium-priority) indications under
7 this scheme, while the use of IVIG in non-toxin-mediated sepsis in the intensive care unit is
8 not recommended. Reflecting this need for ‘IVIG stewardship’ we performed a
9 retrospective study to evaluate our use of IVIG in adult patients referred to our hospital with
10 severe respiratory failure (SRF) requiring extracorporeal membrane oxygenation (ECMO).
11 We specifically focused on the patients with clinically suspected toxin-mediated shock.
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31 Materials and methods

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33 We collected data on patients admitted to St. Thomas’ Hospital, who received ECMO
34 and who were prescribed IVIG between April 2016 and March 2018. Our centre is one of the
35 5 commissioned centres in the UK for adult SRF. We perform over 100 ECMO runs per year.
36 The hospital pharmacy keeps a continuous record of IVIG supplied, this database was cross-
37 referenced to the patients admitted to the ECMO unit. We then performed a retrospective
38 review of prospectively collected case notes in the electronic patient data management
39 systems ICCA (version F0.1, Philips, Amsterdam, Netherlands) and EPR (Clinical Manager
40 iSoft 2004, DXC Technologies, VA, USA) and collected demographics, admission and
41 discharge diagnosis, indication for IVIG, dose received, clinical features suggestive of toxin-
42 mediated disease, immunoglobulin serum levels, microbiology including presence of
43 influenza infection, antibiotic therapy, ECMO configuration, vasopressor dose, organ failure
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score, inflammatory parameters (C-reactive protein (CRP) and procalcitonin (PCT)), arterial lactate levels, adverse effects of IVIG and mortality. Institutional approval for this audit project and waiver of consent was obtained. Data were analyzed using GraphPad Prism 7.0a (GraphPad Software Inc., USA). Data are shown as n (%), mean $\pm$ SD, or as median (IQR) depending on distribution. For comparison between groups, t-test or Mann-Whitney U test was used. For categorical variables, comparisons were made using Fisher's exact test. P < 0.05 was considered statistically significant.

Results

During the first 12 months, 16 patients received a total of 1984 g of IVIG, the following year 25 patients received a total of 3810 g. This represents 2,4 % and 4,7 % of the total of IVIG used in our hospital for those years, respectively. The patients were 41 $\pm$ 15 years, 54% were male. The majority required veno-venous (VV)-ECMO, with 19.5% receiving veno-veno-arterial (VVA)-ECMO and 5% veno-arterial (VA)-ECMO. One patient received IVIG on two separate occasions for two different indications. One patient did not receive the prescribed dose, one patient only received IVIG after ECMO decannulation, one patient received IVIG before he was cannulated four days later. All of these patients are included in the analysis. Non-infective indications such as immune thrombocytopenic purpura and ANCA-associated alveolar hemorrhage were rare in our patient population (n=1 each). A total of 6 patients received IVIG for an infection on the background of immune deficiency (mostly due to immune suppressant medication).

The remainder of IVIG indications (n=34) were prescribed for the "blue" indication of clinically suspected group A streptococcal or staphylococcal disease. In this group, only two patients had a confirmed diagnosis of *S. pyogenes* necrotizing fasciitis or toxic shock

confirmed prior to receiving their first dose of IVIG. The final microbiological diagnosis in this group was group A streptococcal necrotizing soft tissue infection in 2 patients, group A streptococcal TSS in 5 patients, PVL-positive *S. aureus* sepsis in 8 patients (1 with pyomyositis with disseminated disease, the remainder with necrotizing pneumonia), non-PVL-positive *S. aureus* sepsis in 8 patients, pneumococcal septic shock in 3 patients, *P. aeruginosa* in 2 patients, and 1 patient each with meningococcal, *K. pneumoniae* and polymicrobial sepsis. In 3 patients, no etiological microorganism could be identified. All but 3 of these 34 patients received a protein synthesis inhibitor (linezolid or clindamycin) as part of their empirical antibiotic therapy. In this select group of patients, those with a confirmed final diagnosis of group A *Streptococcus* or PVL-positive *S. aureus* were indistinguishable from those with other final diagnoses, except for a predisposing influenza infection and the presence of an often very high procalcitonin level in those with confirmed toxin-mediated disease (**Table 1**).

All 34 patients presented in multiple organ failure with a mean SOFA score of 15 ± 3 . The mean IgG serum level was 6.8 (3.9-9.1) g/dL. One in three died.

In 2 of the 34 patients, an infusion reaction was recorded as an adverse event to IVIG administration. However, when the second dose of IVIG was administered at lower infusion rate, there was no recurrence of this reaction.

Discussion

We report our use of IVIG in a population of critically ill patients requiring ECMO for SRF. The predominant indication for IVIG was presumed toxin-mediated shock, but at admission the microbiological data were unknown to the clinician in virtually all cases. Some patients presented with typical clinical characteristics to suggest the etiology – haemoptysis

1 and cavitating pneumonia in PVL-positive shock - but some patients had atypical
2 presentations with severe shock and in other patients with a necrotizing pneumonia and
3 shock a different etiological microorganism was isolated. The diverse clinical presentations,
4 with the absence of rapid culture results, make it exceptionally challenging to differentiate
5 toxin-mediated disease from other septic shock states. The presence of PVL-producing *S.*
6 *aureus* or group A *Streptococcus* was associated with a very high PCT level, which might be a
7 helpful signpost to the clinician at presentation.
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10 The critical care clinician has to balance restrictive prescribing of IVIG versus its
11 potential benefit in patients with a very high expected mortality. Despite the fact that the
12 patients who received IVIG in our cohort were very ill, the mortality of 35% (12/34) is
13 substantially less than the >90% mortality predicted by the SOFA scores [22, 23].
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16 There are limitations to our study. We did not have data on superantigen production
17 for the *S. aureus* strains, and 3 of the 16 strains were not tested for the production of PVL.
18 The doses of IVIG administered varied: an initial dose of 1-2g/kg could be followed by doses
19 of 0.5 g/kg on the next 2 days or 1-2 g/kg repeat dosing on day 2. Pharmacokinetics of IVIG
20 in patients with extracorporeal support are unknown. There are very limited data on safety
21 and pharmacodynamics effects of IVIG in patients on ECMO. From this limited evidence, it
22 seems that immunoglobulins still exert a measurable biological effect in patients on ECMO
23 [24,25], although the effective dose reaching the patient could be smaller [25], in keeping
24 with potential adsorption of proteins to the ECMO circuit [26]. Also, the volume of
25 distribution in severely septic patients on ECMO will be enlarged [26]. Hence, we suggest to
26 use high doses of 2g/kg as only rare patient adverse effects have been reported attributable
27 to IVIG [24], and in our experience, we have not seen any negative effects of IVIG on the
28 ECMO circuit.
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1 From our study, we conclude that we use IVIG selectively in a population of
2 extremely ill patients, as evidenced by high SOFA scores and vasopressor requirements.
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4 Although not all of our patients present with a 'classical' presentation suggestive of toxin-
5 mediated shock, the initial clinical suspicion was supported by isolation of a toxin-producing
6 organism in more than 40% of our cases. In view of the absence of microbiological
7 confirmation at patient presentation and the need for early intervention, we propose that it
8 is safe and reasonable to use IVIG in a population of acutely ill patients with high SOFA
9 scores, even more so when they have extremely elevated PCT levels, suggestive clinical
10 presentation and confirmed influenza on rapid testing. We use IVIG in these patients as
11 part of a multimodal approach, as recently described [27]. We would argue for a uniform
12 initial dose of 2 g/kg IVIG in these severely ill patients. In the future, IVIG might be
13 substituted by IgM-enriched IVIG [20].
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31 We view these findings as hypothesis-generating, and support the design of a
32 randomized clinical trial in this field. Furthermore, there is an urgent need to improve the
33 rapid identification of toxin-producing organisms and to understand the mechanism of
34 action of IVIG in this patient population better. This future research might enable us to use
35 such a potentially valuable but limited resource better.
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Table

Characteristic	Septic shock, non-PVL or GAS N=20	PVL +ve <i>S. aureus</i> or GAS TSS N=14	p-value
Hemoptysis	6 (30%)	6 (43%)	p=0.49
Cavitation	5 (25%)	5 (36%)	p=0.70
Leukopenia	5 (25%)	6 (43%)	p=0.46
Diarrhea, vomiting	4 (20%)	5 (36%)	p=0.44
Hyperpyrexia	5 (25%)	5 (36%)	p=0.70
Influenza *	5 (25%)	9 (64%)	p=0.04
PCT ≥ 100 ng/mL*	7 (35%)	11 (79%)	p=0.02
CRP (mg/L)	201 (96-360)	266 (194-324)	p=0.25
Lactate (mmol/L)	8.7 $\pm$ 6.4	8.6 $\pm$ 5.2	p=0.95
Vasopressor dose	0.97 $\pm$ 0.68	0.88 $\pm$ 0.53	p=0.69
V(V)A ECMO	4 (20%)	3 (21%)	p=0.99
SOFA score	15 $\pm$ 2.5	15 $\pm$ 3.5	p=0.96
Mortality	9 (45%)	3 (21%)	p=0.28

Table 1. Comparison of patients with confirmed toxin-mediated shock versus patients

with septic shock caused by other micro-organisms. GAS = group A *Streptococcus*, PVL =

Panton-Valentine Leukocidin-positive (PVL +ve) *S. aureus*, PCT = procalcitonin, CRP = C-

reactive protein, vasopressor dose expressed in norepinephrine equivalent dose (sum of

epinephrine and norepinephrine dose rates in mcg/kg/min), N vaso-actives = number of

vasopressors or inotropes (norepinephrine, epinephrine, vasopressin, dobutamine,

levosimendan, milrinone, hydrocortisone), V(V)A ECMO = veno-arterial ECMO or hybrid

veno-veno-arterial ECMO. Data are expressed as number of patients (% of patients), median

(IQR) or mean $\pm$ SD. * Significant difference between groups (p<0.05).

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