UK Health Security Agency

Intravenous immunoglobulin in the treatment of invasive Panton-Valentine Leukocidin Staphylococcus

A rapid systematic review

Contents

Main messages

1. This rapid systematic review (search up to 18 December 2024) identified and summarised evidence relating to the use of intravenous immunoglobulin in hospital in-patients treated for invasive Panton-Valentine Leukocidin *Staphylococcus aureus* (PVL-SA) infection.

2. Seven case reports were identified, each describing individual patients (2 women and 5 men) including a total of 3 children and 4 adults (1 to 8).

3. The case reports described individual children and adults receiving different dosage and frequency of intravenous immunoglobulin alongside antibiotics to treat invasive PVL-SA invasive infections including necrotising pneumonia, epidural abscess, osteoarticular infection, periarticular and perifemoral neck abscesses, psoitis with bacteremia, osteomyelitis, meningitis, sacroiliitis, muscular abscesses, cellulitis, pneumonia, septicaemia, septic shock, lung abscesses. All reported that patients made a full recovery following treatment except for one adult with an extensive medical history who did not survive despite receiving antibiotics and intravenous immunoglobulin.

4. All the case reports had a high risk of bias. They often lacked detailed demographic and clinical information, and did not consistently report dosage or frequency of intravenous immunoglobulin. Case reports rely on individual observation of patients and therefore it is not possible to generalise this evidence-base to all inpatients with PVL-SA receiving immunoglobulin.

5. In summary, the only available evidence was from case reports describing patients in hospital with symptoms of invasive PVL-SA infection (for example, a high fever) and details of their treatment with antibiotics and intravenous immunoglobulin. Some reports gave limited details on dosage and frequency of intravenous immunoglobulin, but they all described the outcome of treatment. Most case reports only noted that intravenous immunoglobulin was used with other antibiotics to treat PVL-SA.

Purpose

The purpose of this rapid systematic review was to identify and summarise the available evidence on the use of intravenous immunoglobulin in the treatment of invasive PVL-SA infection.

The review question was:

1. What is the available evidence on the use of intravenous immunoglobulin in the treatment of invasive PVL-SA?

Methods

A rapid systematic review was conducted following streamlined systematic methods to accelerate the review process. A literature search was undertaken to look for relevant peer-reviewed published research up to 18 December 2024.

The following invasive infections were of interest for this review, as specified by subject matter experts: osteomyelitis, necrotising fasciitis, pyomyositis, septic arthritis, deep seated tissue infections/abscesses, necrotising pneumonia, bacteraemia, abscesses and purpura fulminans. Studies that did not use polymerase chain reaction testing or genomic sequencing to confirm invasive PVL-SA infection in inpatients were excluded from the review. The outcomes of interest for this review were the dose and frequency of use of intravenous immunoglobulin (antibodies from donated blood plasma) and mortality.

A protocol was produced before the literature search was conducted, including the review question, the eligibility criteria, and all other methods. Full details of the methodology are provided in the protocol in Annexe A. There was one deviation from the protocol. In the protocol, it was mentioned that citation search was going to be performed. However, citation searching was not performed in this review.

Screening title and abstract was undertaken in duplicate by 2 reviewers for 20% of the eligible studies, with the remainder completed by one reviewer. Screening full text was undertaken by one reviewer and checked by a second. Data extraction was undertaken by one reviewer and checked by a second.

Risk of bias assessment was conducted in duplicate by 2 reviewers. The JBI tools (9) for prevalence studies, case series and case reports were used for critical appraisal of included studies.

Evidence

In total, 1000 records were screened at title and abstract and 33 records were screened at full text. Of these, 7 records met the inclusion criteria. The PRISMA diagram showing the flow of records through this review is available in Annexe B. Records excluded on full text screening are available with the reasons why in Annexe C.

The included studies were 7 case reports, each of which included only one case (1 to 8). Three case reports were of children (1 girl, 2 boys) (2 to 4) and the other 4 were in adults (1 woman, 3 men) (1, 6 to 8). Only one case report documented the patient's ethnicity (7) and most case reports did not note the country or the time period when cases occurred. Additional details are provided in Table D.1.

Children

Three case reports described children between the ages of 3.6 and 14 years arriving at the general practitioner and later admitted to hospital (2), the emergency department and later admitted to the intensive care unit (3), or in hospital (4) with signs of an infection (such as high fever) and being given antibiotics to treat the symptoms. In addition to antibiotics, intravenous immunoglobulin was given either because it was suspected the patient had developed an invasive infection due to PVL-SA, which was later confirmed with laboratory testing (2), after laboratory tests confirmed presence of PVL-SA (3), or when symptoms suggested an infection, with laboratory testing confirming presence of PVL-SA afterward (4). In one case report of a boy 3 years and 6 months old, intravenous immunoglobulin was given for 6 days, with the dose based on the patient's bodyweight in grams per kilogram, but the patient's weight was not reported (3). The other case report described giving 5 grams for 3 days of intravenous immunoglobulin (without any additional information) suggesting the patient received intravenous immunoglobulin each day for 3 consecutive days; although this was not specifically stated (4). One report did not mention dosage or frequency of intravenous immunoglobulin (2). All patients described in these case reports recovered following administration of antibiotics and intravenous immunoglobulin.

Adults

Four case reports described adults between the ages 19 and 63 years arriving at the emergency department (6, 8) or in hospital (1, 7) with signs of an infection (such as high fever) who were given antibiotics to treat the symptoms. When antibiotics did not completely improve the patient's symptoms (7), intravenous immunoglobulin was given on suspicion that the patient had an invasive PVL-SA infection, later confirmed with laboratory testing (6), or only after laboratory tests confirmed presence of PVL-SA (1, 8).

In one case report, a 49 year old man weighing 74 kilograms was given 600 milligrams for each kilogram of bodyweight once a day for 6 days of intravenous immunoglobulin (1). In another case, the patient received 2 grams of intravenous immunoglobulin for each kilogram of bodyweight across 4 days, but the patient's weight was not reported (7). Two reports did not document dosage or frequency of intravenous immunoglobulin (6, 8). Three out of 4 of the patients described as recovered following administration of antibiotics and intravenous immunoglobulin (1, 6, 7).

One case report described a patient who died after being infected with PVL-SA despite having received antibiotics and intravenous immunoglobulin (8). This patient had an extensive history of medical conditions and was a former smoker. Additional details on the patient's comorbidities are in presented in Table D.1. A medical examination after his death showed he had developed extensive necrotising pneumonia with large abscesses (build-up of pus) in both lungs.

Critical appraisal of evidence

Risk of bias was generally high across all case reports. Most case reports did not provide a detailed description of patients' demographic or clinical information apart from age and sex with one report only describing the patient's medical history. Case reports also did not always provide information on the dosage and frequency of intravenous immunoglobulin.

As case reports are only based on individual patient observations a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment for quality of evidence could not be conducted. Since the evidence comes from case reports describing individual clinical observations, it cannot be generalised to the wider population even if they share similar characteristics.

Health inequalities

The evidence from case reports only included 7 people in total and did not provide a detailed description of patients' demographic details. There was limited information on ethnicity and socioeconomic background and comorbidities of the reported cases. It is therefore not possible to draw meaningful conclusions from the available evidence-base about possible health inequalities in this field of research.

Limitations

This rapid systematic review used streamlined systematic methods to accelerate the review process, so it is possible relevant evidence may have been missed.

This rapid systematic review provides a summary of the available evidence on the use of intravenous immunoglobulin for treating PVL-SA infection, however the only available evidence

was case reports describing individual responses. Case reports are not randomly selected and do not include a comparator. The included case reports reported limited demographic information, and it was not possible to establish whether patients who recovered from the PVL-SA infection was specifically due to the use of intravenous immunoglobulin or to other factors. From this review, it was not possible to know whether intravenous immunoglobulin can improve outcomes in people with PVL-SA. Publication bias is also a concern as case reports with favourable outcome may be more likely to be published. This means this review might have found reports where patients recovered and these were chosen for publication, while reports where patients did not improve might not have been published.

Evidence gaps

There was a lack of high-quality primary research such as experimental or observational studies in the use of intravenous immunoglobulin for treating PVL-SA infection. The evidence exclusively came from case reports within which, demographic details were limited to mostly age and sex and therefore there is a lack of knowledge in patients' profile for whom intravenous immunoglobulin may be useful. Some case reports provided a limited description on using intravenous immunoglobulin for treating PVL-SA as they did not report key details about the reasons for using them or the optimal dosage since the amount and frequency were not always reported. The side- or long-term effects were not routinely reported and therefore there is lack of knowledge whether intravenous immunoglobulin is safe in the short and long-term.

Conclusion

Case reports gave limited detail about the use of intravenous immunoglobulin with only a few studies reporting how much and how often it was used. Some case reports mentioned using intravenous immunoglobulin because the patient's condition became worse or when there was indication the patient had PVL-SA infection or an invasive infection such as necrotising pneumonia. In all cases, patients received intravenous immunoglobulin alongside antibiotics. In all case reports, patients recovered except for one patient with an extensive list of medical conditions did not survive. It was not possible to provide a comprehensive description of participants demographic details because case reports did not provide sufficient information on these factors.

Acknowledgments

We would like to thank colleagues within the All Hazards Public Health Response division who either reviewed or input into aspects of the review.

Disclaimer

UKHSA's rapid systematic reviews and evidence summaries aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, and papers on preprint servers.

Please note that the reviews:

- use accelerated methods and may not be representative of the whole body of evidence publicly available
- have undergone an internal independent peer review but not an external peer review
- are only valid as of the date stated on the review

In the event that this review is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

References

1. Catena V and others. 'Necrotizing pneumonia caused by panton-valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* (MSSA)' Infezioni in Medicina 2012: volume 20, pages 205 to 210
2. Fitzgerald F and others. 'Back pain in a previously healthy teenager' BMJ Case Reports 2013
3. Moumile K and others. 'Severe osteoarticular infection associated with Panton-Valentine leukocidin-producing *Staphylococcus aureus*' Diagnostic Microbiology and Infectious Disease 2006: volume 56, pages 95 to 97
4. Ogata H and others. 'Psoitis and multiple venous thromboses caused by Panton Valentine Leukocidin-positive methicillin-sensitive *Staphylococcus aureus* in a 12 year old girl: a case report' Journal of Infection and Chemotherapy 2019: volume 25, pages 630 to 634
5. Peetermans M and others. 'Use of Intravenous Immunoglobulins in Patients with Suspected Toxin-Mediated Shock Requiring Extracorporeal Membrane Oxygenation' Shock 2020: volume 54, issue 2, pages 209 to 212
6. Saha B and others. 'The case of the vanishing lung' Chest 2016: volume 150, page 402A
7. Salliot C and others. 'Panton-Valentine leukocidin-producing *Staphylococcus aureus* infections: report of 4 French cases' Scandinavian Journal of Infectious Diseases 2006: volume 38, issue 3, pages 192 to 195
8. Vayalumkal JV and others. 'Necrotizing pneumonia and septic shock: suspecting CA-MRSA in patients presenting to Canadian emergency departments' CJEM Canadian Journal of Emergency Medical Care 2007: volume 9, issue 4, pages 300 to 303
9. JBI. 'JBI Critical appraisal tools' 2020

Annexe A. Protocol

Review question

The review question is:

1. What is the available evidence on the use of intravenous immunoglobulin in the treatment of invasive Panton-Valentine Leukocidin Staphylococcus?

A search for primary evidence to answer this review question will be conducted up to 18 December 2024.

Eligibility criteria

Table A.1. Inclusion and exclusion criteria

	Included	Excluded
Population	Adults and children with laboratory confirmed (for example polymerase chain reaction test or genomic sequencing) invasive Panton-Valentine Leukocidin Staphylococcus being treated as hospital inpatients Invasive will be defined as: • osteomyelitis • necrotising fasciitis • pyomyositis • septic arthritis • deep-seated tissue infections/ abscesses • necrotising pneumonia • bacteraemia • abscesses • purpura fulminans	Adults and children without invasive Panton-Valentine Leukocidin Staphylococcus
Context	Any	
Settings	Hospital	• laboratories • community

	Included	Excluded
Intervention or exposure	Intravenous immunoglobulin (on its own or with co-intervention), of any dose or frequency to treat invasive Panton-Valentine Leukocidin Staphylococcus	Immunoglobulin given by any other route
Comparator	Comparator not required	
Outcomes	Frequency of immunoglobulin use Mortality (as reported by the study)	
Language	English	Any other language
Date of search	Up to 18 December 2024	
Study design	Experimental studies including randomised-controlled trials, quasi-experimental studies, cross-over designs, before-and-after studies. Observational studies including cohort studies, case-control studies, case series and case reports.	• modelling studies • qualitative studies • mixed methods • reviews (all types)
Publication type	Peer-reviewed published research	• conference abstracts or presentations • editorials • letters • news articles • grey literature • preprints

Identification of studies

The following databases and trial registries will be searched for studies published up to 18 December 2024: Ovid Medline, Ovid Embase, Cochrane Central Register of Controlled Trials, Scopus and CINAHL The search strategy is presented below.

Backwards and forwards citation searching will be carried out using references that are included at full text screening as seed papers. Citation searching will use Lens.org via CitationChaser.

Screening

Title and abstract screening will be undertaken in duplicate by 2 reviewers for at least 20% of the eligible studies, with the remainder completed by one reviewer. Disagreement will be resolved by discussion or with involvement of a third reviewer where necessary.

Screening on full text will be undertaken by one reviewer and checked by a second.

Results of citation searching will be screened by one reviewer.

Data extraction

Demographic information and study characteristics for each study will be extracted and reported in tabular form. Data extraction will be undertaken by one reviewer and checked by a second. Information to be extracted where available will include:

- demographics of the study population including age, sex, ethnicity, and comorbidities
- study characteristics including study design, sample size, and study period
- dosage and frequency of intravenous immunoglobulin

Risk of bias assessment

We will perform risk of bias assessment at the primary study level using the relevant JBI checklist. Risk of bias will be assessed by 2 reviewers independently with disagreements resolved through discussion or with a third reviewer.

Quality of evidence

The quality of evidence identified within this review will be assessed, if available evidence allows, using a modified version of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (2). Quality of evidence will be assessed at the outcome level, and be rated as one of 4 levels:

- very low (the true effect is probably different from the estimated effect)
- low (the true effect might be different from the estimated effect)
- moderate (the true effect is probably close to the estimated effect)
- high (the authors are confident that the true effect is similar to the estimated effect)

The quality of evidence will be assessed for each outcome across 4 domains:

1. Risk of bias: where results may not represent the true effect because of limitations in the design or conduct of the study. This will be measures as described under Risk of bias assessment.

2. Inconsistency: where studies show different effects for the same outcome of interest. This will be assessed where there are 2 or more studies measuring the same outcome. Inconsistency will be rated down if the point estimates are not similar, or the confidence intervals do not overlap. If there is only one study for the outcome of interest, then inconsistency will not be assessed. Inconsistency will be assessed by one reviewer and checked by a second.

3. Indirectness: where elements of the study differ from the intended elements in the review question (for example, the outcome of interest has not been directly measured). This will be rated down if the population, intervention, comparator, or outcome of interest have not been directly measured. Indirectness will be assessed by one reviewer and checked by a second.

4. Imprecision: a measure of how uncertain the estimate is. Imprecision will be rated down if the confidence intervals cross the line of no effect, or if the reviewer judges that the confidence intervals are overly wide and so the true effect is likely to be different at the upper versus the lower end of the confidence interval. Imprecision will be assessed by one reviewer and checked by a second.

If the studies only report count data without effect size measures like odds ratios (OR) or relative risks (RR), a GRADE assessment will not be possible.

Synthesis

If data is presented in a consistent format between studies, a narrative synthesis will be produced to describe the results from this review. The number of studies, the number of participants in each study, effect size and variance and a summary of the risk of bias across studies will be summarised and presented. Alternatively, if data is too heterogeneous, a narrative summary of each study will be provided.

Health inequalities

Where available, data for children aged 17 years or below will be presented separately to that of individuals aged 18 years or above.

Search strategy

Ovid MEDLINE(R) ALL (1946 to 18 December 2024)

1. Leukocidins/ (1,750)
2. Leukocidin*.tw,kf. (2,244)
3. leucocidin*.tw,kf. (566)
4. Panton Valentine.tw,kf. (2,340)
5. leukotoxi*.tw,kf. (1,111)
6. leucotoxi*.tw,kf. (73)
7. PVL.tw,kf. (5,159)
8. LukS.tw,kf. (376)
9. LukF.tw,kf. (333)
10. Luk pv.tw,kf. (49)
11. Bacterial Toxins/ and (exp Staphylococcal Infections/ or exp Staphylococcus aureus/) (3,592)
12. or/1-11 (9,927)
13. immunoglob*.tw,kf. (189,679)
14. immune glob*.tw,kf. (4,192)
15. immuneglob*.tw,kf. (23)
16. exp Immunoglobulins/ (1,016,606)
17. alphaglob*.tw,kf. (14)
18. (antibod* adj5 intravenous*).tw,kf. (2,040)
19. endobulin*.tw,kf. (19)
20. flebogamma dif.tw,kf. (5)
21. gamimmune.tw,kf. (8)
22. gamimune.tw,kf. (38)
23. gammagard.tw,kf. (76)
24. gammonativ.tw,kf. (4)
25. gamunex.tw,kf. (59)
26. globulin.tw,kf. (46,417)
27. ivig.tw,kf. (10,637)
28. intraglob*.tw,kf. (66),
29. intravenous ig.tw,kf. (184)
30. iveegam.tw,kf. (3)
31. privigen.tw,kf. (62)
32. sandoglob*.tw,kf. (146)
33. venimmune.tw,kf. (0)
34. venoglob*.tw,kf. (17)
35. or/13-34 (1,117,349)
36. 12 and 35 (696)

Embase (1974 to 18 December 2024)

1. Leukocidin/ (1,014)
2. Panton Valentine Leukocidin/ (2,765)
3. Leukocidin*.tw,kf. (2,755)
4. leucocidin*.tw,kf. (652)
5. Panton Valentine.tw,kf. (2,913)
6. leukotoxi*.tw,kf. (1,187)
7. leucotoxi*.tw,kf. (82)
8. PVL.tw,kf. (7,882)
9. LukS.tw,kf. (491)
10. LukF.tw,kf. (417)
11. Luk pv.tw,kf. (56)
12. bacterial toxin/ and (exp Staphylococcus infection/ or exp Staphylococcus aureus/) (1,544)
13. or/1-12 (12,419)
14. immunoglob*.tw,kf. (243,398)
15. immune glob*.tw,kf. (5,812)
16. immuneglob*.tw,kf. (60)
17. exp immunoglobulin/ (635,508)
18. alphaglob*.tw,kf. (37)
19. (antibod* adj5 intravenous*).tw,kf. (2,854)
20. endobulin*.tw,kf. (316)
21. flebogamma dif.tw,kf. (49)
22. gamimmune.tw,kf. (50)
23. gamimune.tw,kf. (412)
24. gammagard.tw,kf. (840)
25. gammonativ.tw,kf. (65)
26. gamunex.tw,kf. (411)
27. globulin.tw,kf. (52,494)
28. ivig.tw,kf. (25,653)
29. intraglob*.tw,kf. (266)
30. intravenous ig.tw,kf. (318)
31. iveegam.tw,kf. (115)
32. privigen.tw,kf. (522)
33. sandoglob*.tw,kf. (1,303)
34. venimmune.tw,kf. (2)
35. venoglob*.tw,kf. (290)
36. or/14-35 (756,643)
37. 13 and 36 (339)

CINAHL

Date of search: 19 December 2024

#	Query	Results
S1	Leukocidin*	291
S2	leucocidin*	80
S3	leukotoxi*	48
S4	leucotoxi*	5
S5	"Panton Valentine"	349
S6	PVL	760
S7	LukS	65
S8	LukF	11
S9	"Luk pv"	3
S10	(MH "Bacterial Toxins+")	12,865
S11	(MH "Staphylococcal Infections+")	12,003
S12	(MH "Staphylococcus Aureus+")	12,572
S13	S11 OR S12	18,507
S14	S10 AND S13	333
S15	immunoglob*	33,058
S16	"immune glob*"	1,135
S17	immuneglob*	0
S18	(MH "Immunoglobulins+")	77,506
S19	alphaglob*	1
S20	(antibod* N5 intravenous*)	264
S21	endobulin*	1,560
S22	"flebogamma dif"	0
S23	gamimmune	1,560
S24	gamimune	1,560
S25	gammagard	1,567
S26	gammonativ	1,560
S27	gamunex	8
S28	globulin	5,969
S29	ivig	2,657
S30	intraglob*	2

#	Query	Results
S31	"intravenous ig"	1,585
S32	iveegam	1,560
S33	privigen	1,570
S34	sandoglob*	1
S35	venimmune	1,560
S36	venoglob*	1
S37	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S14	1,190
S38	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	89,496
S39	S37 AND S38	32

Cochrane Central Register of Controlled Trials

Date of search: 19 December 2024

ID	Search	Hits
#1	MeSH descriptor: [Leukocidins] explode all trees	9
#2	Leukocidin*	21
#3	leucocidin*	5
#4	leukotoxi*	6
#5	leucotoxi*	0
#6	"Panton Valentine"	21
#7	PVL	480
#8	LukS	43
#9	LukF	0
#10	"Luk pv"	0
#11	MeSH descriptor: [Bacterial Toxins] explode all trees	4,278
#12	MeSH descriptor: [Staphylococcal Infections] explode all trees	1,562
#13	MeSH descriptor: [Staphylococcus aureus] explode all trees	1,195
#14	#12 OR #13	2,052
#15	#11 AND #14	22
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #15	554

ID	Search	Hits
#17	immunoglob*	17,692
#18	immune glob*	5423
#19	immuneglob*	8
#20	MeSH descriptor: [Immunoglobulins] explode all trees	40,092
#21	alphaglob*	73
#22	(antibod* NEAR/5 intravenous*)	710
#23	endobulin*	10
#24	flebogamma dif	20
#25	gamimmune	6
#26	gamimune	16
#27	gammagard	36
#28	gammonativ	3
#29	gamunex	37
#30	globulin	4,435
#31	ivig	1,812
#32	intraglob*	15
#33	intravenous ig	2,083
#34	iveegam	5
#35	privigen	55
#36	sandoglob*	45
#37	venimmune	3
#38	venoglob*	15
#39	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	49,417
#40	#16 AND #39	32

Limited to trials only: 11 results.

Scopus

Date of search: 19 December 2024

TITLE-ABS-KEY(Leukocidin*) OR TITLE-ABS-KEY(leucocidin*) OR TITLE-ABS-KEY("Panton Valentine") OR TITLE-ABS-KEY(leukotoxi*) OR TITLE-ABS-KEY(leucotoxi*) OR TITLE-ABS-KEY(PVL) OR TITLE-ABS-KEY(LukS) OR TITLE-ABS-KEY(LukF) OR TITLE-ABS-KEY("Luk pv")

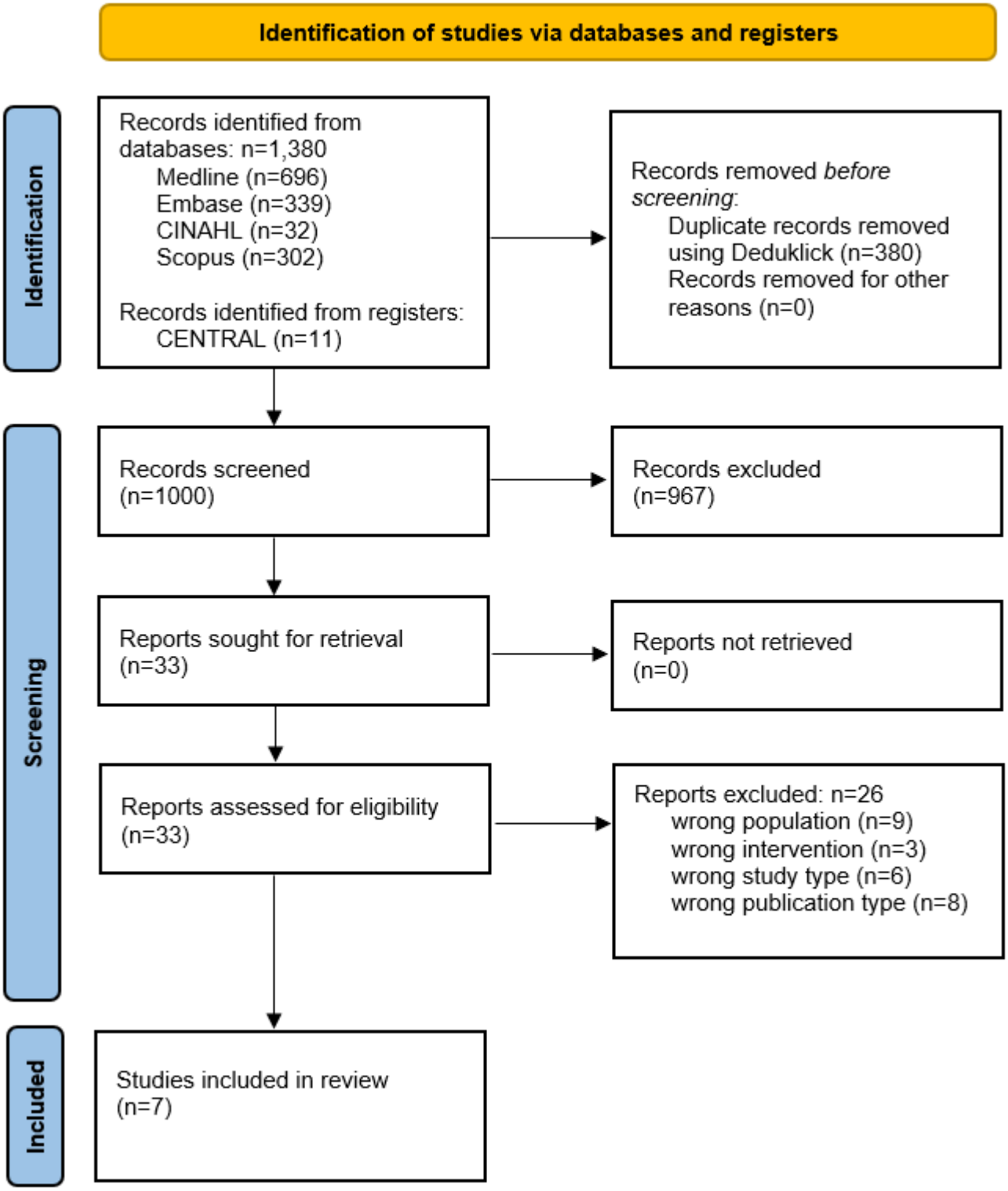
AND

TITLE-ABS-KEY(immunoglob*) OR TITLE-ABS-KEY("immune glob*") OR TITLE-ABS-KEY(immuneglob*) OR TITLE-ABS-KEY(alphaglob*) OR TITLE-ABS-KEY((antibod* W/4 intravenous*)) OR TITLE-ABS-KEY(endobulin*) OR TITLE-ABS-KEY("flebogamma dif") OR TITLE-ABS-KEY(gamimmune) OR TITLE-ABS-KEY(gamimune) OR TITLE-ABS-KEY(gammagard) OR TITLE-ABS-KEY(gammonativ) OR TITLE-ABS-KEY(gamunex) OR TITLE-ABS-KEY(globulin) OR TITLE-ABS-KEY(ivig) OR TITLE-ABS-KEY(intraglob*) OR TITLE-ABS-KEY("intravenous ig") OR TITLE-ABS-KEY(iveegam) OR TITLE-ABS-KEY(privigen) OR TITLE-ABS-KEY(sandoglob*) OR TITLE-ABS-KEY(venimmune) OR TITLE-ABS-KEY(venoglob*)

302 results.

Annexe B. Study selection flowchart

Figure B.1. PRISMA diagram



Text version of figure B.1. PRISMA diagram

A PRISMA diagram showing the flow of studies through this review, ultimately including 7 studies.

From identification of studies via databases and registers, n=1,380 records identified from databases:

- Ovid Medline (n=696)
- Ovid Embase (n=339)
- CINAHL (n=32)
- Scopus (n=302)
- CENTRAL (n=11)

From these, records removed before screening:

- duplicate records removed using Deduklick (n=380)
- records removed for other reasons (n=0)

n=1000 records screened, of which n=967 were excluded, leaving n=33 papers sought for retrieval, of which n=0 were not retrieved.

Of the n=33 papers assessed for eligibility, n=26 reports were excluded:

- wrong population (n=9)
- wrong intervention (n=3)
- wrong study type (n=6)
- wrong publication type (n=8)

n=7 papers included in the review.

Annexe C. Excluded full texts

Wrong population (9 studies)

Agwu A and others. 'Cholera-like diarrhea and shock associated with community-acquired methicillin-resistant Staphylococcus aureus (USA400 clone) pneumonia' Pediatric Infectious Disease Journal 2007: volume 26, pages 271 to 273

Banthia S and others. 'A fatal case of necrotizing pneumonia caused by community-associated methicillin-resistant Staphylococcus aureus' Infectious Diseases in Clinical Practice 2005: volume 13, pages 132 to 138

Barry PJ and others. 'Panton-Valentine Leukocidin-positive Staphylococcus aureus: A potentially significant pathogen in cystic fibrosis' Paediatric Respiratory Reviews 2014: volume 15, pages 22 to 25

Capasso L and others. 'An unusual aggressive presentation of late onset sepsis due to Staphylococcus aureus MRSA producing Panton-Valentine leucocidin in preterm neonate' Acta Biomedica 2021: volume 92

Gilaberte Y and others. 'Correlation between serum 25-hydroxyvitamin D and virulence genes of Staphylococcus aureus isolates colonizing children with atopic dermatitis' Pediatric Dermatology 2015: volume 32, pages 506 to 513

Masaki K and others. 'Fatal fulminant pneumonia caused by methicillin-sensitive Staphylococcus aureus negative for major high-virulence factors following influenza B virus infection' American Journal of Case Reports 2015: volume 16, pages 454 to 458

McAdams RM and others. 'Necrotizing Staphylococcal pneumonia in a neonate' Journal of Perinatology 2005: volume 25, pages 677 to 679

Peetermans M and others. 'Use of Intravenous Immunoglobulins in Patients with Suspected Toxin-Mediated Shock Requiring Extracorporeal Membrane Oxygenation' Shock 2020: volume 54, issue 2, pages 209 to 212

Satia I. 'Not your typical pneumonia' Clinical Medicine, Journal of the Royal College of Physicians of London 2013: volume 13, pages 206 to 210

Wrong intervention (3 studies)

Kim YH and others. 'The First Neonatal Case of Panton-Valentine Leukocidin-Positive Staphylococcus aureus Causing Severe Soft Tissue Infection in Korea' Pediatric Infection and Vaccine 2023: volume 30, pages 152 to 158

Krutikov M and others. 'Necrotizing pneumonia (aetiology, clinical features and management)' Current Opinion in Pulmonary Medicine 2019: volume 25, pages 225 to 232

Yoo R and others. 'ST714-SCCmec type IV CA-MRSA isolated from a child with recurrent skin and soft tissue infections in South Korea: A case report' Paediatric Infection and Vaccine 2016: volume 23, pages 62 to 66

Wrong study type (6 studies)

Clark J. 'A brief review of Panton-Valentine Leukocidin producing staphylococcal infections in the intensive therapy unit' Current Anaesthesia and Critical Care 2008: volume 19, pages 330 to 332

Haggar A and others. 'Dual effects of extracellular adherence protein from Staphylococcus aureus on peripheral blood mononuclear cells' Journal of Infectious Diseases 2005: volume 192, issue 2, pages 210 to 217

Morgan MS. 'Diagnosis and treatment of Panton-Valentine Leukocidin (PVL)-associated staphylococcal pneumonia' International Journal of Antimicrobial Agents 2007: volume 30, issue 4, pages 289 to 296

Spencer DA and others. 'Necrotising pneumonia in children' Paediatric Respiratory Reviews 2014: volume 15, pages 240 to 245

Wenzel RP and others. 'Community-acquired methicillin-resistant Staphylococcus aureus (MRSA): new issues for infection control' International Journal of Antimicrobial Agents 2007: volume 30, issue 3, pages 210 to 212

Wood JB and others. ‘Commercial Intravenous Immunoglobulin Preparations Contain Functional Neutralizing Antibodies against the Staphylococcus aureus Leukocidin LukAB (LukGH)’ Antimicrobial Agents and Chemotherapy 2017: volume 61, issue 11, page 11

Wrong publication type (8 studies)

Ek T and others. 'PVL-positiva Staph aureus gav nekrotiserande pneumoni' Lakartidningen 2007: volume 104, pages 509 to 513

Hampson FG and others. 'Disseminated sepsis due to a Panton-Valentine Leukocidin producing strain of community acquired meticillin resistant Staphylococcus aureus and use of intravenous immunoglobulin therapy' Archives of Disease in Childhood 2006: volume 91, issue 2, page 201

Lees N and others. 'Combination ecmo and cytokine adsorption therapy for severe sepsis with cardiogenic shock and ards' Critical Care Medicine 2015: volume 1, page 311

Liu J and others. 'Overview of Panton-Valentine Leukocidin-expressing Staphylococcus aureus pneumonia and its therapeutic strategy' Advances in Biology 2022: volume 1, pages 123 to 151

Peetermans M and others. 'IVIG administration in ECMO patients with suspected toxin-mediated shock' Perfusion (Germany) 2019: volume 34, page 102

Saha B and others. 'The case of the vanishing lung' Critical Care Medicine 2015: volume 1, page 181

Vincent F and others. 'Community infection at Staphylococcus aureus with Panton Valentine Leucocidin in New Caledonia polyvalent ICU: a descriptive study' Annals of Intensive Care. Conference: French Intensive Care Society International Congress 2020: volume 10

Wood JB and others. 'Commercial intravenous immunoglobulin (IVIG) preparations contain functional neutralizing antibodies against the Staphylococcus aureus cytotoxin LukAB' Open Forum Infectious Diseases. Conference: ID Week 2016: volume 3

Annexe D. Data extraction tables

Abbreviations: DNA = deoxyribonucleic acid, g = gram, kg = kilogram, mg = milligram.

Table D.1. Data extraction table of case reports

Study, study design	Country, time period, settings	Population and medical history	Diagnostic test Panton-Valentine Leukocidin infection type	Intervention	Outcomes
Catena 2012 (1)	Italy, April 2010 Hospital	Population: • n=1 • man • 49 years old • ethnicity not reported Medical history: • no predisposing factors • previously healthy	Polymerase chain reaction: • amplification of Panton-Valentine Leukocidin S and F genes Spa Typing: • locus: Accessory Gene Regulator type IV • spa type: 159 • clonal complex Necrotising pneumonia	Piperacillin/ Tazobactam: • 45 grams every 8 days Levofloxacin: • 500 milligrams/day Rifampicin: • 600 milligrams every 12 hours Oxacillin: • 12 grams/day Meropenem: • 1 gram every 6 hours Rifampicin: • 600 milligrams every 12 hours	Intravenous immunoglobulin infusions: • 6 days at 600 mg/kg/day Case recovered
Fitzgerald 2013 (2)	not reported General practitioner	Population: • n=1 • 14 years old • boy • ethnicity not reported Medical history: Previously healthy with a history of contact sports and discitis	Polymerase chain reaction Necrotising pneumonia Epidural abscess	Flucloxacillin and clindamycin with immediate dose of gentamicin Linezolid Dosage and frequency not reported	Intravenous immunoglobulin infusions (dosage and frequency not reported) Case recovered
Moumile 2006 (3)	France,	Population: • n=1 • 3 years and 6 months old	Multiplex polymerase chain reaction:	Oxacillin: • 100 mg/kg per day	Intravenous immunoglobulin: • 6 amounts of 3 g/kg

Study, study design	Country, time period, settings	Population and medical history	Diagnostic test Panton-Valentine Leukocidin infection type	Intervention	Outcomes
	Time period not reported Emergency department	• boy • ethnicity not reported Medical history: • previously healthy	• genes coding for exotoxins C, L, M, O, and P, and Panton-Valentine leucocidin Osteoarticular infection Periarticular and perifemoral neck abscesses	Cefotaxime: • 100 mg/kg per day Gentamicin: • 5 mg/kg per day Later changed to: Oxacillin: • 265 mg/kg per day Gentamicin: • 4.5 mg/kg per day Ciprofloxacin: • 45 mg/kg per day Imipenem: • 50 mg/kg per day) Fosfomycin: • 210 mg/kg per day Ciprofloxacin: • 45 mg/kg per day	Case recovered
Ogata 2019 (4)	Country not reported Time period not reported Hospital	Population: • n=1 • 12 years old • girl • ethnicity not reported Medical history: • previously healthy	Multilocus sequence typing: • sequencing for *S. aureus*-specific staphylococcal protein A (spa) typing Tests: • Coagulase typing • *Staphylococcus aureus* toxin identification Toxins • toxic shock syndrome toxin 1	Ampicillin Cefotaxime Vancomycin Cefazolin • 100 mg/kg/day q8h) • added later: clindamycin (40 mg/kg/day q8h)	Intravenous immunoglobulin: • 5g x 3 days Case recovered

Study, study design	Country, time period, settings	Population and medical history	Diagnostic test Panton-Valentine Leukocidin infection type	Intervention	Outcomes
			• Exfoliative toxin • Panton-Valentine leukocidin • Staphylococcal enterotoxin • Arginine catabolic mobile element by polymerase chain reaction Results: • sequence type=2149 (a single-locus variant of ST8) • spa type=t008 • Coagulase type=III Psoitis with bacteremia Osteomyelitis	Rifampicin • (600 mg/day q24h)	
Saha 2016 (6)	Country not reported Time period not reported Emergency department	Population: • n=1 • 63 years old • woman • ethnicity not reported Medical history: • asthma	Genetic testing Methicillin-resistant *Staphylococcus aureus* Necrotising pneumonia	Ceftriaxone Azithromycin Linezolid Clindamycin Nafcillin Dosage and frequency not reported	Intravenous immunoglobulin: (dosage and frequency not reported) Case recovered
Salliot 2006 (7)	Country not reported Time period not reported Hospital	Population: • n=1 • 19 years old • man • Caucasian Medical history: • previously healthy	Polymerase chain reaction Enterotoxins = B, M, O, G, I, N Meningitis Epidural abscess Sacroiliitis Muscular abscesses Cellulitis Pneumonia Septicaemia	Cefotaxime (later changed to fusidic acid and pefloxacin) Fosfomycin, fusidic acid, pefloxacin for 3 months Pefloxacin and fusidic acid for 3 more months dosage not reported	Intravenous immunoglobulins: • 2g per kg across 4 consecutive days Case recovered

Study, study design	Country, time period, settings	Population and medical history	Diagnostic test Panton-Valentine Leukocidin infection type	Intervention	Outcomes
Vayalumkal 2007 (8)	Canada Time period not reported Emergency department	Population: • n=1 • 48 years old • man • ethnicity not reported Medical history: • diet-controlled type 2 diabetes mellitus • hypertension • coronary artery spasm • depression • congenital single kidney	DNA fingerprint analysis with pulsed-field gel electrophoresis and multilocus sequence typing Staphylococcal Cassette Chromosome mec Leukocidin F-Panton-Valentine Leukocidin S-Panton-Valentine Community-associated methicillin-resistant *Staphylococcus aureus* Necrotising pneumonia Septic shock Lung abscesses	Eftriaxone Azithromycin Vancomycin Dosage and frequency not reported	Intravenous immunoglobulin (dosage and frequency not reported)

Annexe E. Risk of bias assessment

Table E.1. Risk of bias assessment for case reports

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Comments
Catena and others, 2012	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Q2: family history, including relevant genetic information not stated Q7: no adverse events or harms of intervention reported
Fitzgerald and others, 2013	Yes	No	Yes	Yes	No	Yes	No	Yes	Q2: family history including relevant genetic information and psychosocial history not stated Q5: dosage and frequency of IV immunoglobulin not stated Q7: no adverse events or harms of intervention reported
Moumile and others, 2016	Yes	No	Yes	Yes	No	Yes	No	Yes	Q2: family history including relevant genetic information and psychosocial history not stated Q5: frequency of IV immunoglobulin not stated Q7: no adverse events or harms of intervention reported
Ogata and others, 2019	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Q2: family history including relevant genetic information and psychosocial history not stated Q7: no adverse events or harms of intervention reported
Saha and others, 2016	No	No	Yes	Yes	No	Yes	No	Yes	Q2: family history including relevant genetic information and psychosocial history not stated Q7: no adverse events or harms of intervention reported
Salliot and others, 2006	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Q2: family history including relevant genetic information and psychosocial history not stated Q7: no adverse events or harms of intervention reported
Vayalumkal and others, 2007	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Q5: dosage and frequency of IV immunoglobulin not stated Q7: no adverse events or harms of intervention reported

Critical appraisal was done using the JBI checklist for case reports |# JBI, 2024|.

List of questions:

Q1: Were patient’s demographic characteristics clearly described?
Q2: Was the patient’s history clearly described and presented as a timeline?
Q3: Was the current clinical condition of the patient on presentation clearly described?
Q4: Were diagnostic tests or assessment methods and the results clearly described?
Q5: Was the intervention(s) or treatment procedure(s) clearly described?
Q6: Was the post-intervention clinical condition clearly described?
Q7: Were adverse events (harms) or unanticipated events identified and described?
Q8: Does the case report provide takeaway lessons?

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