Risk of infection in adult patients with primary immune thrombocytopenia (ITP)
a systematic review
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Risk of infection in adult patients with Primary Immune Thrombocytopenia (ITP): A systematic review

Abstract

Introduction: Primary immune thrombocytopenia (ITP) is a bleeding disorder characterized by autoimmune destruction and impaired production of platelets. Immunosuppressive drugs are the main treatment and may increase risk of infection.

Areas covered: This systematic review included studies incorporating adult patients with primary ITP and infectious outcomes. Studies comparing risk of infection with the general population were included as primary and studies without this comparison were considered secondary. Three primary and ten secondary studies were included. The main findings: 1-year adjusted relative-risk of infection was 4.5 (95% CI, 3.3 - 6.1) fold elevated compared to the general population. When comparing splenectomized with non-splenectomized ITP patients, the +1-year adjusted relative-risk of infection was 4.0 (95% CI, 2.8 - 5.6). The unadjusted 5-year mortality rate-ratio for infection-related deaths was 6.0 (95% CI, 3.0 - 11.8) in one study, and the hazard ratio was 2.4 (95% CI, 1.0 - 5.7) for fatal infections in another.

Expert opinion: This review emphasizes that patients with ITP have increased risk of infection. Since ITP is a benign hematologic disease, it is important to assess the extent and causes of infection in the clinical care and considerations before initiating treatment. More homogeneous studies are needed on this topic.

Keywords: Corticosteroids, immune thrombocytopenia, immunosuppression, infections, ITP, mortality, review, risk
1. Introduction

Primary immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by autoantibody-mediated premature platelet destruction and suboptimal thrombopoiesis due to immunological inhibition of the megakaryocytes [1-3].

The incidence of primary ITP is 2 to 5 per 100,000 person-years and increases with age [4-6]. The diagnosis is based on isolated thrombocytopenia defined as a platelet count < 100 x 10⁹/L and the absence of underlying secondary causes resulting in thrombocytopenia. When thrombocytopenia is caused by underlying disease, e.g. other autoimmune disease or infection, the disease is classified as secondary ITP [4,7].

Primary ITP can be classified as acute (disease duration < 3 months), persistent (> 3-12 months) or chronic (> 12 months) [7,8]. Patients with primary ITP may present as asymptomatic with routine blood sampling revealing thrombocytopenia or as symptomatic patients with skin bleeding such as petechiae and bruising. Mucous membrane bleedings such as epistaxis and bleeding from gums are also frequent, whereas severe bleedings in gastrointestinal tract, urinary tract or intracranial hemorrhage are rare [9]. In addition, patients with primary ITP also have an increased risk of thromboembolism, reduced quality of life and increased fatigue [10-13].

Treatment of primary ITP should be individualized and based on multiple factors such as symptoms, age, lifestyle and platelet count, with platelet counts < 20 x 10⁹/L often requiring treatment [4,7,14].

Treatment aims at preventing severe bleeding and ensuring good quality of life, which requires that the decision to initiate treatment is balanced between benefits and potential side effects. The risk of severe bleeding was assessed in a systematic review containing 10,908 patients and found to be 1.4% (95% CI, 0.9 - 2.1) for intracerebral hemorrhage and 9.6% (95% CI, 4.1 - 17.1) for non-intracerebral hemorrhage [4]. The adjusted 5-year relative risk (RR) for intracranial bleeding was 3.2 (95% CI, 1.2 - 9.0) in a population-based cohort compared 1:10 with the general population [15].

First-line treatment is high-dose corticosteroids for 2-3 weeks. With response, treatment should be tapered off over 6-8 weeks, but some patients may benefit from continuous low-dose prednisolone, e.g. concomitantly with another primary drug. An alternative option is high dose dexamethasone for 4 days, especially if rapidity of platelet count response is of high value [4,7,16-18].
Use of intravenous polyvalent immunoglobulin (IVIg) or IV anti-D will induce a rapid but transient elevation of the platelet count and can be appropriate in patients at high risk of bleeding or with active bleeding as rescue therapy [4,7,19,20]. Platelets can be transfused in patients with active critical bleeding, but the effect is even more transient and remains as a last resort in most cases [7]. Subsequent therapies include rituximab, which has been used off-label since 2000 [21]. Rituximab causes B-cell depletion and consequently inhibits production of autoantibodies and the stimulation of T-cells, but may also induce hypogammaglobulinemia [22,23]. Rituximab is often used in combination with dexamethasone, with a dose of 375 mg/m² or 100 mg/m² weekly for 4 weeks and dexamethasone 40 mg per day for 4 days. Other subsequent and novel therapies include thrombopoietin receptor agonists (TPO-RAs), stimulating thrombopoiesis and inhibiting the phagocytosis of thrombocytes [7,24].

Splenectomy is a surgical option to improve platelet count [7]. The purpose of splenectomy is to remove an anatomical site for platelet destruction and possibly also reduce autoantibody production. However, splenectomy is associated with lifelong increased risk of infection, especially against encapsulated bacteria [25]. Therefore, lifelong antibiotic preparedness is required. Laparoscopic splenectomy may be preferred over open surgery, and the peri-operative mortality is estimated to be 0.2% [26,27].

Other medical immunosuppressive therapies with less robust evidence include mycophenolate, azathioprine, cyclosporin A, cyclophosphamide, danazol, dapsone and vinca alkaloids [7].

Since immunomodulating therapy is the cornerstone in the treatment of primary ITP, it is generally considered that treatment increases the risk of infections in this disease [28]. Several studies have evaluated the efficacy and safety of different therapies, including the risk of infection, other studies have evaluated the risk of infection compared to different subpopulations with primary ITP [29-33]. However, to the best of our knowledge very few studies have evaluated the risk of infection in patients with ITP compared to the general population.

This lack of data prompted us to elucidate the risk of infection in adult patients with primary ITP through a systematic review of published data.
1.1 Aim
The aim of this systematic review was to present, compare and evaluate the current knowledge on this topic, based on results from studies focusing on the overall risk of infection in adult patients with primary ITP compared to the general population. Such knowledge would support physicians in order to advance management of the disease.

2. Methods

2.1 Eligibility criteria
This systematic review was conducted in accordance with The PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [34].

The research question (PICO(S)) that drove the selection of studies was: **What is the risk of infection in adult patients with primary ITP compared to the general population?**

Predefined inclusion and exclusion criteria were: Patients (P) defined as adults diagnosed with primary ITP, the intervention (I) was omitted since the overall risk of infection was assessed, comparison (C) was defined as the general population. Knowing that there is little evidence in this field, additional relevant studies without comparisons were also included as secondary studies. The main outcome (O) of interest was risk of infection. The study types (S) of interest were randomized controlled trials, cohorts and case-controls. Studies with at least 10 patients were included. For all studies a follow-up period of at least 6 months was required to ensure the order of causality between exposure (primary ITP) and outcome (infection). Furthermore, risk of infection should be reported as a separate outcome in the studies. Exclusion criteria were secondary ITP if these patients were inseparable from patients with primary ITP.

2.2 Information sources and search strategy
To identify eligible studies for this systematic review, the PubMed database was searched. The final literature search was performed on March 25, 2021. The first block consisted of primary ITP synonyms. The second block consisted of “infections” and an elaborating list of common infections. The blocks were combined with the Boolean operator AND. Medical Subject Headings [MeSH Terms] and Keywords were used in the blocks. The complete detailed literature search is provided in
2.3 Study selection and data collection process
Covidence.org was used as systematic review software to keep track of the flow of studies [35]. Two investigators (MS and EAP) performed the title and abstract screening independently. Studies that fulfilled inclusion criteria were extracted for full-text reading. Any disagreements were discussed until consensus was obtained. If necessary, the other co-authors (HF and NM) were consulted to make the final decision. Data from the included articles were independently extracted by two investigators (MS and EAP), and there was no discrepancy of the extracted data.

2.4 Data items
The extracted study characteristics included year of publication, study design, data source, focus of the study, potential comparison, population size, enrollment period, study duration and age of the included patients. The extracted results included findings related to infection, including total number of infections, absolute risk (AR), relative risk (RR), incidences, hazard ratios (HR), information regarding mortality related to infection and how infection was identified in the studies. Moreover, the site of infection was extracted.

2.5 Risk of bias in individual studies
The Newcastle-Ottawa scale [36] was used for detecting bias on a study level. The scale is a quality instrument to assess bias in observational studies with scores ranging from 0-9. A higher score indicates lower risk of bias in the study.

3. Results

3.1 The study selection
A total of 2447 publications were identified through the PubMed database and qualified for screening (Figure 1). Three studies were removed due to duplication. During the title and abstract
screening 2214 publications were excluded, most because they were not relevant to the research question (466 publications), many were case reports (554 publications), had a pediatric population (348 publications), or focused on secondary ITP e.g. helicobacter pylori, human immunodeficiency virus, hepatitis virus, cytomegalovirus, epstein-barr virus or drug-induced ITP (445 publications). In addition, 401 publications were disqualified because of incorrect setting or wrong study design.

The remaining 230 studies were assessed for eligibility via full-text review, leaving 12 studies that fulfilled inclusion criteria. The most frequent reason for exclusion at this stage of the screening was “wrong study design” (Figure 1). One additional study was identified within the reference lists of the 12 included studies. The citation search in the database Web of Science did not identify further studies. The characteristics of the primary and the secondary articles are summarized in Tables 1 and 2, respectively.

3.2 Characteristics of the primary studies
The three primary studies (Table 1) [15,37,38] were all population-based cohorts based on health registries and medical records. Nørgaard et al. [15] compared the long-term clinical outcomes, including overall and cause-specific mortality and rates of infections of all incident chronic primary ITP patients with the general population. Frederiksen et al. [37] assessed the long-term overall and cause-specific mortality among patients with primary ITP compared to the general population. Thomsen et al. [38] investigated the risk of infection associated with splenectomy of all causes, including splenectomy for primary ITP. To separate potential effects of surgery and the disease itself, the study assembled two additional comparison groups: An appendectomy group and a matched-indication group (e.g. patients with primary ITP but without splenectomy) [38].

3.3 Characteristics of the secondary studies
The ten included secondary studies (Table 2) were generally very heterogeneous and therefore the results were difficult to compare [21,22,39-46]. However, all studies contained aspects of infection in patients with primary ITP. One study by Moulis et al., 2015 [21], a nested case-control study assessed the risk of corticosteroid-related infection among patients with primary ITP. Cases were ITP patients with infection, and controls were ITP patients without infection. Thai et al. [39] composed a single-center cohort study, assessing long-term incidence of splenectomy complications in patients with primary ITP. Splenectomized patients were matched 1:1 with non-splenectomized
patients. In the population-based cohort study by Moulis et al., 2017 [40] the risk factors of infection in non-splenectomized patients with primary ITP were assessed using health registries and cox models. A cohort study by Portielje et al. [41] assessed the mortality and morbidity of patients with primary ITP also using health registries and medical records. The mortality was compared with the general population, but the mortality due to infection was not displayed, and therefore this study was not included as a primary study. Hu et al. [42] investigated factors associated with the risk of short-term (6 months) infection in patients with primary ITP using medical records. Palandri et al. [43,44] contributed with two studies focusing on elderly patients with primary ITP. The study from 2019 [43] assessed the management of elderly patients with primary ITP in a multicenter cohort study. The study from 2018 [44] was a single-center cohort study investigating the impact of age on primary ITP characteristics including response and complications rates. Moulis et al., 2013 [45] compared the outcomes in patients with primary ITP treated with rituximab versus splenectomy, using medical records, health registries and phone interviews. Vianelli et al. [46] composed a multicenter cohort study assessing the outcome of splenectomized patients with primary ITP. Finally, Deshayes et al. [22] assessed the long-term safety and efficacy of rituximab in patients with primary ITP in a prospective multicenter cohort study using health registries.

3.4 Risk of bias

Using the Newcastle Ottawa scale [36] on the three primary studies [15,37,38] all three studies were assessed a high score (8 out of 9 stars) indicating low risk of bias within the studies. All studies missed a star, because none of the studies demonstrated that outcome of interest (infection) was not present at the start of study. All studies received a star for representativeness of the exposed cohort, because they were all somewhat representative of the average primary ITP patients in the community. Nørgaard et al. [15] only included chronic ITP patients defined as patients with at least 2 hospital-based diagnoses of primary ITP over a period of ≥ 6 months. Thus, potentially excluding less severe forms of primary ITP. The registry used by Frederiksen et al. [37] only allowed to include hospitalized patients from 1973 and both hospitalized and outpatients from 1983, thus potentially including a subgroup with more adverse outcome in the beginning of the study. Thomsen et al. [38] included primary ITP patients with a splenectomy diagnosis, and therefore, for the purpose of this review, created a subpopulation since splenectomy is more frequently used in younger and more
refractory patients [43,45]. The elaborated quality assessment of the three main studies is provided in the supplementary material.

3.5 Risk of infections - Primary articles (Table 3)
The study by Nørgaard et al. [15] found that 62 (15.2%) patients with chronic primary ITP had ≥ 1 hospital registered infection, compared with 178 (4.4%) individuals among matched comparisons. The adjusted 1-year RR of infection was 4.5 (95% CI, 3.3 - 6.1) for patients with chronic ITP compared with the general population. Similarly, Thomsen et al. [38] found an increased risk of infection, with an adjusted RR of 14.2 (95% CI, 4.3 - 46.1) for hospital contact due to infection for splenectomized ITP patients 91-365 days postoperatively compared to the general population. The adjusted RR decreased for both studies in the subsequent follow-up period. Nørgaard et al. [15] reported an adjusted RR of 1.8 (95% CI, 1.3 - 2.5) during year 2-5 and Thomsen et al. [38] reported an adjusted RR 4.0 (95% CI, 2.8 - 5.6) in the period exceeding 365 days. Of note, Thomsen et al. [38] also compared the risk of infection in splenectomized patients with primary ITP with the “matched-indication cohort” and found an adjusted RR 1.4 (95% CI, 1.0 - 2.0).

3.6 Infection-related mortality - Primary articles (Table 3)
Nørgaard et al. [15] found significantly increased 5-year infection-related mortality among patients with primary ITP compared with the general population. The unadjusted 5-year mortality rate ratio (MRR) was 6.0 (95% CI, 3.0 - 11.8) for infection-related deaths. The adjusted 5-year MRR was not reported in this study. Frederiksen et al. [37] found that the adjusted HR of mortality due to infection was 2.4 (95% CI, 1.0 - 5.7) for patients with primary ITP compared with the general population.
3.7 Incidence of infection - Secondary articles (Table 3)

The incidence of infections varied between the studies. The incidence of severe infections was 2/100 patient-years in the study focusing on rituximab effect and toxicity [22]. This incidence was comparable with the results from the multicenter cohort study of elderly ITP patients [43], in which it was 3.9/100 patient-years. Both studies [22,43] defined severe infection according to National Cancer Institute Common Terminology Criteria for Adverse Events as grade > 3 [47]. Moulis et al., 2017 [40] found the incidence of serious infection (defined as hospitalizations with a primary infection diagnosis registration) to be 6.3/100 patient-years and for non-serious infections 100.5/100 patient-years. This study used out-of hospital antibiotic dispensing as a proxy for non-serious infection, potentially also including antibiotics prescribed for prophylaxis. This may account for the variation between the incidence rate for grade >2 infection (i.e. requiring systemic treatment) where Palandri et al., 2018 [44] reported an incidence of 1.55/100 patient-years (information of obtained data was not further elucidated in the article).

3.8 Immunosuppressive treatment and infection

Several treatment strategies for primary ITP are based on immunosuppressive treatments. A case-control designed study [21] where cases were ITP patients with severe infection and controls were ITP patients without infection, found that corticosteroids were the leading factor associated with occurrence of severe infection. The regression model that fitted the data best included corticosteroid exposure during the month before the first infection with an OR of 2.48, (95% CI, 1.61 - 3.83) [21]. However, corticosteroid exposure was significantly associated with infection in a time period up to six months before infection. Additionally, odds of severe infection increased with daily prednisone or equivalent doses of 5-10 mg and ≥ 10 mg with ORs of 2.09 (95% CI, 1.17 - 3.71) and 1.99 (95% CI, 1.26 - 3.17) using < 5 mg daily as reference category. The risk of infection was mainly associated with recent or current exposure to corticosteroid [21].

Similar findings were found in another study [40] where the risk of serious infection was assessed. Exposure to corticosteroids had the highest HRs of the investigated covariates (age, mucosal bleeding, chronic pulmonary disease, chronic kidney disease, exposure to rituximab, exposure to corticosteroids, exposure to IVIg, pneumococcal vaccine and influenza vaccine), with HR 3.83 (95% CI, 2.76 - 5.31). Of note, the HR of IVIg was found to be 2.98 (95% CI, 1.86 - 4.77). This presumption that IVIg is associated with an increased risk of infection may be due to
channeling bias, since IVIg is used in patients with severe disease. Moreover, the HR of rituximab was 2.60 (95% CI, 1.67 - 4.03) as the third highest of the tested variables. When assessing the risk of non-serious infection, the exposure to corticosteroid, IVIg and rituximab were again significantly associated with increased risk.

Deshayes et al. [22] investigated rituximab and related reactions. Gammaglobulin levels were available in 142 patients. Hypogammaglobulinemia (< 5g/L) after a median of 25 months developed in five patients and was symptomatic in one patient who developed pneumocystis jirovecii pneumonia. Multivariate analysis in Hu et al. [42] revealed that a lower absolute lymphocyte count at diagnosis (< 1 X 10^9/L) was an independent risk factor for infection in ITP with OR of 1.93 (95% CI, 1.03 - 3.60).

Several studies found that stable responders and less severe disease were associated with lower risk of infection [42,44,46]. Hu et al. [42] found a tendency towards patients with primary ITP with more severe disease, had a higher risk of infection, however, this was not significant. In line with this, Vianelli et al. reported that a stable response to splenectomy was significantly associated with a decreased rate of infection (P=0.004) and additionally that patients with infection received a significantly higher number of therapies [46]. Similarly, Palandri et al., 2018 [44] found that a more severe disease presentation with low platelet count and active hemorrhages requiring therapy was significantly associated with infections.

The findings concerning splenectomy are only of some consistency. The largest and the study of best quality is Thomsen et al. [38], where the risk of infection increased 14.2-fold compared with the general population during the first year. In the study by Thai et al. [39] it was found that the number of patients with at least one bacterial infection did not differ significantly between the splenectomized patients and the controls. However, splenectomized patients experienced more severe infections, because 100% of infected patients in the splenectomized group were hospitalized compared to 61.5% of the controls with infection (P=0.002). In contrast, in the study by Palandri et al., 2019 [43] univariate analysis found a decreased risk of infection associated with splenectomy. However, this was not significant in the multivariable analysis. This finding was probably due to confounding bias, because older patients (>75 years) were less frequently splenectomized.

In the study by Moulis et al., 2013 [45], there was no difference in the frequency of hospitalization between the rituximab and the splenectomized group.
3.9 Site of infection - Primary and secondary articles

The studies that described the site of infection consistently reported pulmonary infection as the primary site. The proportion of pulmonary infection varied from 33% to 54% among ITP patients with infections [15,21,22,37-40,42-46]. Second most common site of infection varied between the studies. Hu et al. [42], Palandri et al., 2018 [44] and Palandri et al., 2019 [43] found that urinary tract infection was the second most common infection with proportions of 17.8%, 16.7%, and 11.3% respectively. Contrary to that, Nørgaard et al. [15] found that sepsis (11.3%) was the second most common infection. Lastly Moulis et al., 2015 [21] found that gastrointestinal infection was the second most common site accounting for 16.8%. Two studies registered that 6.8% and 14.3% of the serious infections were opportunistic [22,40].

Only one study [21] displayed the proportion of bacterial and viral infections. Infections were distributed with 10.4 % bacterial, 6 % viral, 3.5 % fungal, 0.6% parasitic. However, the codes of infections corresponded mostly to infection localization rather than to the microorganism in cause. Predominant bacterial infections in the studies were gram-negative bacillus [21], staphylococcus aureus [42] and streptococcus pneumoniae [39] while viral agent as varicella-zoster [21,42,43] and influenzae virus[43] accounted for most viral infections.

4. Discussion

Using a matched cohort design, Nørgaard et al. [15] found a substantially increased risk of infection among patients with primary chronic ITP, which was 4.5-fold elevated compared with the general population during the first year. In the long-term follow-up period (2-5 years), patients with primary chronic ITP continued to have an 80% higher risk of infection.

The two studies [15,37] which presented a mortality rate due to infection among patients with primary ITP compared with the general population, both presented an elevated mortality risk ranging from 2.4 to 6 times higher than the general population.

This review incorporated a broad spectrum of infectious results. Unfortunately, the available studies were generally very different and very few studies compared the results with the general population. It was only Nørgaard et al. [15] which displayed data that allowed us to answer the research
question. Hence this was the only study that investigated the risk of infection in patients with ITP compared with the general population. However, the remaining studies included in this review contained important aspects of infection in patients with primary ITP. In Frederiksen et al. [37], the risk of infection was not reported. However, mortality related to infection was reported, and therefore this study provided information about the most severe and thus fatal infections. Thomsen et al. [38] reported the risk of infection in the subpopulation of splenectomized ITP patients. However, it is also important to assess the risk for this population since splenectomy remains a second-line treatment option.

As mentioned, the three primary studies [15,37,38] may have selected a subpopulation of patients with primary ITP with more severe disease (supplementary material), thus potentially overestimating the risk of infection. On the other hand, the platelet cut-off for allowing an ITP diagnosis was changed from \( < 150 \times 10^9/L \) to \( < 100 \times 10^9/L \) in 2009 when standards and terminology in ITP were changed [8]. The primary studies extracted their data before this change, therefore potentially leading to the inclusion of patients with less severe disease. This may underestimate the risk of infection since patients with higher platelet count are unlikely to receive immunosuppressive drugs. Further, patients with primary ITP may experience increased surveillance and a lower threshold for hospital contact compared to the general population, which would also overestimate the risk of infection. However, mortality related to infection increased compared to the general population. This argues against the notion that increased surveillance in patients with primary ITP leads to hospitalization for less severe infections.

The studies included as secondary studies [21,22,39-46] are even more heterogeneous, however almost all are cohort studies.

It is challenging to infer an overall conclusion of these secondary studies since the populations, the inclusion periods, the follow-up, the comparisons, the interventions, the enrollment periods and the platelet cut-offs differ. Further, the definition of primary versus secondary ITP differs, e.g. the study by Hu et al. [42] included 8.8% with Evans syndrome among patients with primary ITP. It was equally challenging to separate results between adults and children in some studies. The study population in Thai et al. [39] had a median age of 37 years ranging between 3-92 years. The proportion of children was not reported. However, the French National Referral Center for Adult Cytopenias was used as the data source, and therefore the study was included since it was assumed
that the number of children was negligible. Similarly, the study by Vianelli et al. [46] was included since only 10% of the patients were under the age of 16 years and due to the overall paucity of data. Therefore, especially the secondary studies can be used to assess an overall tendency of infectious risk.

The studies included as primary studies relied on unselected population-based data with complete follow-up and matched comparisons from the general population. We believe that this comparison group is the most relevant when assessing the “natural” risk of infection and least biased to inform clinicians and decisions.

The search string for this systematic review was inclusive in order to obtain all relevant studies. Doubt about the relevance of a study automatically led to full-text review. The predefined limitation of study population (>10 patients) may compromise the study, because this will exclude some case reports. This will weaken the study, especially since primary ITP is a rare disease. On the other hand, case reports are subject to bias, due to the study design, and such studies are even more heterogeneous.

This review indicates an increased risk of infection in patients with primary ITP. The underlying cause of the increased infection was not the main focus of this review. However, several of the included studies presented explanations of the increased risk. Thomsen et al. [38] stated that all-cause splenectomized patients had a higher risk of infection, and some of this risk was due to underlying conditions and not to splenectomy alone. In a retrospective cohort by Ekstrand et al. [48] it was found that patients with primary ITP had an increased risk of infection even before their diagnosis. Another retrospective cohort found that low platelet count was independently correlated with an increased risk of infection [28]. This could indicate that infection is not solely caused by the immunomodulation treatment but may also be a consequence of the autoimmune disease itself. A possible explanation for this could be the role of thrombocytes in early immunological responses [49]. The theory of thrombocytes not only serving as anuclear cells contributing to hemostasis, but more advanced cells involved in immunological responses has gradually been well established over recent times [50,51]. Thrombocytes interacting with leukocytes, both directly in the forming of platelet-leukocyte aggregates and indirectly with the secretion of signaling agents attracting other immune cells when detecting signs of infection [52]. A lack of thrombocytes could affect these
crucial processes negatively, delaying or weakening an immune response. On the other hand, results from several studies indicate that different treatments contribute to the increased risk of infection and that patients with more severe or non-responding disease requiring multiple therapies were at increased risk of infection [21,22,39,40,42,44,46]. The relative contribution to the risk of infection - of the autoimmune process on one hand and the immunosuppressive treatment on the other, cannot be deduced from our findings.

The increased risk of infection was comparable to results from studies investigating other autoimmune diseases - systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). A meta-analysis [53] investigating the risk of infections in adult patients with SLE found a significantly increased RR 2.96 (95% CI, 1.28 - 6.83) for overall severe infection of patients with SLE compared with the general population. Similar findings were found when investigating RA. A prospective cohort study found a standardized proportional mortality ratio of 3.7 (95% CI, 0.9 - 8.3) of infectious causes of death in patients with RA in comparison to the general population [54]. More recent studies supported this tendency. A case-control study found that glucocorticoids were associated with infection in older patients with RA [55]. A systematic review and meta-analysis assessed the association of infection in patients with RA exposed to glucocorticoid compared to patients who were not exposed to glucocorticoids [56]. A RR of 1.67 (95% CI, 1.49 - 1.87) was generated by the observational studies in the metaanalysis [56]. A study of causes of death in patients with RA [57] found that infectious causes are increasing, and the study raised the question whether this association was caused by more vigorous immunosuppressive treatment, as recommended by recent guidelines [58,59]. However, as for the studies investigating ITP, none of the studies were able to determine the relative contribution of the causes, the disease itself and the immunosuppressive treatment.

In the study by Portielje et al. [41], more patients died due to infection than due to hemorrhage, emphasizing that it is important to improve understanding of the underlying cause of the increased risk of infection in patients with primary ITP. This will be valuable information for physicians considering the different ITP treatment options and for shared decision making with patients.
5. Conclusion

In conclusion, this systematic review indicates that adult patients with primary ITP have an increased risk of severe infection and suffer an increased risk of fatal infections compared to the general population. Further, the research suggests that patients with primary ITP also have an increased risk of non-severe infections. The cause of the increased risk is probably due to the immunosuppressive treatment and the disease itself but the relative effect of each is unknown. Physicians should be aware of the most common infections such as pneumonia, urinary tract infections, gastrointestinal infections, but even critical infections such as sepsis and severe opportunistic infections can occur. The comprehensive literature search revealed sparse evidence to answer the research question. Therefore, a more systematic surveillance and capture of infectious episodes in these patients to advance management and improve risk-benefit knowledge of different ITP treatment options is needed.

6. Expert opinion

This review illustrates that patients with ITP have an increased risk of infection compared to the general population, which is in line with the general assumption among hematologists. It is generally considered that the immunosuppressive treatment of ITP increases the risk of infections. Furthermore, this review raises the question whether the disease itself, the autoimmune process, contributes to the increased risk of infection. However, this assumption is still controversial or at least not generally well-investigated, and a possible correlation needs to be investigated further in the future. Given that the disease itself contributes to increased risk of infection, it is of great interest to determine the relative contribution of each factor, the disease itself and the immunosuppressive treatment. Furthermore, the next question to be answered is whether the risk from the disease and the risk from treatment are additive or synergistic. These future studies could lay the foundation of a discussion of the current order of treatment lines as these are rapidly changing in current years along with the introduction of more novel and targeted treatments (e.g. TPO-RAs and fostamatinib) not exhibiting the same amount of immunosuppressive effect. However, it may still be difficult to assess causality in the question since many patients with ITP have need of treatment, especially patients with severe chronic and relapsing/refractory ITP (e.g. older patients), where the course of the disease
in itself might be an expression for a deeper dysfunction in the immune system and hence risk of infection [60].

The study by Hu et al. [42] states that a lower absolute lymphocyte count at diagnosis (< 1 X 10^9/L) was an independent risk factor for infection in patients with ITP. In the future, absolute lymphocyte count could be a parameter to include in the choice of first-line treatment since low absolute count lean towards choosing other therapies than immunosuppressive drugs, e.g. TPO-RAs. On the other hand, American Society of Hematology guidelines for immune thrombocytopenia [4] note that 6.9% of patients treated with TPO-RAs also experience infections, even though the mechanism of action does not interfere with the immune system. Besides that, even though TPO-RAs is considered a safe treatment after >10 years on the market, it remains a relatively newly introduced treatment with issues regarding risk of thrombosis and dietary restrictions. However, new generation TPO-RAs are also emerging [61].

Overall increased surveillance and focus on infection, through more exhaustive anamnesis of the patient's history of infection and other risk factors of infection e.g. pulmonary disease or diabetes could contribute to advanced management of the disease. Increased focus on shared decision-making is desirable, since several studies demonstrate that physicians and patients have different views on limitation of the disease and side-effect of treatment [12,62,63]. Guidry et al. investigated the differences between hematologists and patients’ perspectives on the side-effects of corticosteroid treatment for ITP. The study illustrated great distinction in the perception of the frequency and extent of corticosteroid side-effects among the hematologists and the patients. The study revealed that patients more frequently thought that the side-effects caused “a lot of bother”. On the other hand, hematologists were more worried about serious bleeding compared to the patients [62]. This demonstrates the importance of effective communication between the patient and hematologist. Unfortunately, the concern about infection was not investigated. However, it seems reasonable to assume that there could be a distinction between hematologists and patients’ perspectives here as well. Therefore, a discussion about the risk of infection between the hematologist and patient is essential. One way to promote communication about infections could be routine questionnaire surveys. This could promote shared decision making and help close the gap between the patients- and the hematologist perceptions. In addition, it can promote the education of patients.
6.1 Five-year view

In the five-year perspective we envisage more systematic screening and focus on risk of infection among patients with ITP, including patients more in shared decision making, identification of potential biomarkers for infection post-diagnostic of ITP, earlier targeted treatment and upcoming treatments to improve clinical care.

7. Article highlights

- Studies in this field are limited and those available are very heterogeneous and therefore difficult to compare.
- Adult patients with primary ITP have increased risk of severe and fatal infection compared to the general population.
- The decision to initiate treatment should be balanced between benefits and potential side-effects, including the risk of infection, therefore it is important to know the extent of infection among patients with ITP.
- Research suggests that infection is not solely caused by the immunomodulation treatment but may also be a consequence of the autoimmune disease itself.
- The relative contribution to the risk of infection of the autoimmune process on one hand and the immunosuppressive treatment on the other, is not determined yet.

8. Funding in the included studies

The included studies were funded by both private and public foundations. Moulis et al. [40,45] and Portielje et al. [41] did not provide information about funding.

9. Funding

This paper was not funded.

10. Author Contributions

H Frederiksen and N Mannering conceptualized the idea for the study. All co-authors participated in the study’s design. M Sandvad and EA Pedersen performed the literature search, the screening and wrote the first draft of the article. All four authors contributed to writing subsequent drafts. All authors
have read and agreed to the submitted version of the manuscript. M Sandvad and EA Pedersen contributed equally and shared co-first authorship.

11. Declaration of interest

H Frederiksen has received funding outside of this work from Novartis, Alexion, AbbVie and Gilead. N Mannering has received funding outside of this work from Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

12. Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

13. References

Papers of special interest have been highlighted (⋆) and papers of considerable interest have been highlighted (⋆⋆).


Figure 1. PRISMA flowchart. The search string identified 2447 studies. Of these, three studies were removed due to duplication and 2214 were excluded after title and abstract screening, leaving 230 studies accessible for eligibility via full-text review. 218 were then excluded in this process, mostly due to wrong study design. One additional study was identified via reference lists of the included studies. This yielded a total of 13 studies included in this systematic review, distributed with three primary and ten secondary studies.
Table 1. Characteristics of the primary studies. The extracted data are: Year of publication, country, study design, focus, matched comparisons, population size, data source, enrollment period, study duration and age of included patients with primary immune thrombocytopenia (ITP).

| Author (Year)                          | Country           | Study design                      | Focus                                                                 | Comparisons                                                                 | Population                                                                 | Data source                               | Enrollment period (year) | Study duration, follow-up | Age (years) | Ref. |
|----------------------------------------|-------------------|-----------------------------------|                                                                      |                                                                            |                                                                           |                                         |                           |                            |                  |     |
| Nørgaard et al. (2011) Denmark          |                   | Population-based cohort study     | Long-term clinical outcomes among patients with chronic ITP          | Matched 1:10 with the general population                                  | $N_{	ext{ITP}}$: 407  
$N_{	ext{matched}}$: 4069                                             | Health registries and medical records                                     | 1996 - 2007                  | Median follow-up: 55.2 months (0-138 months)  
Median follow-up comparison: 58.8 months (range, 0-139.2 months) | 55.3% ≤ 60 years old       | [15] |
| Frederiksen et al. (2014) Denmark       |                   | Population-based cohort study     | Long-term overall and cause-specific mortality among patients with ITP | Matched 1:10 with the general population                                  | $N_{	ext{ITP}}$: 221  
$N_{	ext{matched}}$: 2210                                             | Health registries and medical records                                     | 1973 - 1995                  | Median follow-up: 197.3 months (IQR: 85.4-283.2 months) | Median age: 54.9 years   | [37] |
| Thomsen et al. (2009) Denmark           |                   | Population-based cohort study     | Risk for hospital contact with infection associated with splenectomy (all indication) | Matched with the general population 1:10, an appendectomized cohort 1:5, matched indication cohort 1:5  
$N_{	ext{splenectomy ITP}}$: 269  
$N_{	ext{matched population}}$: 2690  
$N_{	ext{appendectomy}}$: 1292  
$N_{	ext{matched indication}}$: 1345                                 | Health registries and medical records                                     | 1996 - 2005                  | Median follow-up: 26.4 months                              | Median age: 47 (IQR: 28-61) | [38] |

IQR: Inter quartile range
Table 2. Characteristics of the secondary studies. Extracted data: Year of publication, country, study design, main focus, comparisons, population size, data source, enrollment period, study duration and age of included patients with primary ITP. The studies are presented based on relevance.

<table>
<thead>
<tr>
<th>Author (Year) Country</th>
<th>Study design</th>
<th>Focus</th>
<th>Comparisons</th>
<th>Population</th>
<th>Data source</th>
<th>Enrollement period (year)</th>
<th>Study duration, follow-up</th>
<th>Age, years</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulis et al. (2015) France</td>
<td>Nested case-control study</td>
<td>The risk of corticosteroid-related severe infection among ITP patients, adjusted for other treatment</td>
<td>Cases: ITP patients with infection &lt;br&gt; Controls: ITP patients without infection &lt;br&gt; Matched 1:2</td>
<td>Nitr: 161&lt;br&gt;Ncontrol: 321</td>
<td>Health registries and medical records</td>
<td>2009 - 2012</td>
<td>Mean follow-up: 18.5 ± 6.8 months</td>
<td>Mean age: 57.6 (± 21.3)</td>
<td>[21]</td>
</tr>
<tr>
<td>Thai et al. (2016) France</td>
<td>Single-center cohort study</td>
<td>Long-term incidence of splenectomy complications in patients with primary ITP, comparing ITP patients with or without splenectomy</td>
<td>Matched 1:1</td>
<td>Nspleenectomized: 83&lt;br&gt;Nspleenectomized: 83</td>
<td>Health registries, medical records and phone interview (patient and/or general practitioner)</td>
<td>1990 - 2004</td>
<td>Median follow-up: 192 months (range 0.5-528)</td>
<td>Median age: 57 (range 3-92)</td>
<td>[39]</td>
</tr>
<tr>
<td>Moses et al. (2017) France</td>
<td>Population-based cohort study</td>
<td>The risk factors for serious and non-serious infections, in non-splenectomized ITP patients</td>
<td>No comparisons</td>
<td>Nspleenectomized: 1805</td>
<td>Health registries</td>
<td>2009 - 2012</td>
<td>Mean follow-up: 18.5 ± 6.8 months</td>
<td>Median age: 60.1</td>
<td>[40]</td>
</tr>
<tr>
<td>Hu et al. (2014) Taiwan</td>
<td>Cohort study</td>
<td>Determine which factors are associated with the risk of short-term infection in patients with ITP</td>
<td>No comparisons</td>
<td>Nitr: 239</td>
<td>Medical records</td>
<td>1997 - 2011</td>
<td>Median follow-up: 19.36 month (range 0.1-155.3 months)</td>
<td>Median age: 61 (range 18-97)</td>
<td>[42]</td>
</tr>
<tr>
<td>Palandrì et al. (2019) Italy</td>
<td>Multicenter cohort study</td>
<td>The impact of very old age (≥75 years) on ITP features at diagnosis including infectious complications</td>
<td>No non-exposed cohort, but sub-grouped into two age-categories: &lt;br&gt; Age: 60 – 74 years &lt;br&gt; Age: ≥ 75 years</td>
<td>Nspleenectomized: 451&lt;br&gt;Nage: 60-74: 258&lt;br&gt;Nage: ≥ 75: 193</td>
<td>Medical records</td>
<td>2000 – 2019</td>
<td>Median follow-up: 56.4 months (range 1-271.2 months)</td>
<td>Median age: 71.1 (range 60-91.5)</td>
<td>[43]</td>
</tr>
<tr>
<td>Moses et al. (2013) France</td>
<td>Cohort study</td>
<td>Comparing outcomes in ITP patients treated with either rituximab or splenectomy</td>
<td>No non-exposed cohort, but two different therapy groups: rituximab vs. splenectomy</td>
<td>Nspleenectomized: 105&lt;br&gt;Nrituximab: 43&lt;br&gt;Nspleenectomized: 62</td>
<td>Health registries, medical records and phone calls to patient and/or general practitioner</td>
<td>1997 – 2010</td>
<td>Mean follow-up: Splenectomy: 100.8 ± 56.4 months &lt;br&gt;Rituximab patients 2002 – 2011</td>
<td>Mean age ± SD: &lt;br&gt;Splenectomy: 38.5 ± 14.1 &lt;br&gt;Rituximab: 36.2 ± 22.8 months</td>
<td>[45]</td>
</tr>
<tr>
<td>Vianelli et al. (2013) Italy</td>
<td>Multicenter cohort study</td>
<td>The outcome of patients who underwent splenectomy for ITP</td>
<td>No comparisons</td>
<td>Nitr: 233</td>
<td>It cannot be determined which data source the study used. However, it may indicate health registries</td>
<td>1959 – 2001</td>
<td>Median follow-up: 240 months (range 120-516)</td>
<td>Median age: 30.5 (range 1.74) (10% under the age of 16 years)</td>
<td>[46]</td>
</tr>
</tbody>
</table>
Data collected from Italy and Sweden

Deshayes et al. (2019)
France

Prospective multicenter cohort study

Long-term safety and efficacy of rituximab in ITP

No comparisons for infection outcome

Nov 248
Health registries
2010 - 2012
Median follow-up: 68.4 months (range 53.3-78.5 months)
Mean age: 51 ± 20 years

SD: Standard deviation
Table 3. Results of infectious outcomes for primary and secondary studies. Available infectious outcomes including absolute risk (AR), relative risk (RR), odds ratio (OR), incidence rates, how infection was identified, total number of infections and mortality related to infection were extracted. The studies are presented based on relevance.

<table>
<thead>
<tr>
<th>Table 3. Results of infectious outcomes for primary and secondary studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary studies</strong></td>
</tr>
<tr>
<td><strong>Absolute risk</strong></td>
</tr>
<tr>
<td>ARITP (year)</td>
</tr>
<tr>
<td>15.2% *</td>
</tr>
<tr>
<td><strong>Relative risk and Odds ratio</strong></td>
</tr>
<tr>
<td>RRa, 1-year</td>
</tr>
<tr>
<td>5.9 (95% CI, 3.3-6.1) *</td>
</tr>
<tr>
<td><strong>Incidence rates</strong></td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td><strong>How infection was identified</strong></td>
</tr>
<tr>
<td>≥1 hospital contact for infection (inpatient or outpatient)</td>
</tr>
</tbody>
</table>
### Total Infections

<table>
<thead>
<tr>
<th>Splenectomy: 18 patients (22%) had a total of 26 infections Controls: 12 patients (14.5%) had a total of 13 infections</th>
</tr>
</thead>
<tbody>
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<td>-</td>
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</table>

<table>
<thead>
<tr>
<th>59 (23.8%) had a total of 103 infections</th>
</tr>
</thead>
</table>

### Mortality

<table>
<thead>
<tr>
<th>5-years infection-related mortality: Patients with ITP: 4.2 (95% CI, 2.4%–7.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparisons: 0.7% (95% CI, 0.5–1.1%)</td>
</tr>
<tr>
<td>5-years unadjusted mortality: 6.0 for infection-related deaths (95 CI, 3.0–11.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The adjusted hazard ratio: 2.4 (95% CI, 1.0–5.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection related death among controls (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5 (3.6%) died of infection in the splenectomy cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (2.2%) died of infection during the first 2 years</td>
</tr>
<tr>
<td>10 (4.2%) died of infection. 9 of them died within 1 year of ITP diagnosis</td>
</tr>
<tr>
<td>8 (1.8%) died of infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5 (2%) died of infection, 3 of them occurred 12 to 14 months after rituximab infusion, and the last two occurred after 24- and 49 months after Rituximab infusion</th>
</tr>
</thead>
</table>

### Ref.

| [15] |
| [17] |
| [18] |
| [23] |
| [39] |
| [40] |
| [41] |
| [42] |
| [43] |
| [44] |
| [45] |
| [46] |
| [22] |
Risk of infection in adult patients with Primary Immune Thrombocytopenia (ITP): A systematic review

Supplementary material

Search string

This document contains the complete literature search as listed below. The search was conducted using the PubMed database on March 25, 2021. The search string contained Medical Subject Heading [MeSH Terms] and keywords. Quotation marks were used to search for phrases where the automatic translation into MeSH terms was not desired. No truncation was used. The first block consisted of synonyms of ITP e.g. “immune thrombocytopenic purpura” and combined with the Boolean operator OR to expand the search. The second block consisted of an elaborating list of common infections and were also combined with OR. The two blocks were combined with the Boolean operator AND. For a better overview, the individual keywords are listed in the table below.


Table with the individual keywords

<table>
<thead>
<tr>
<th>Block 1:</th>
<th>Block 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura, thrombocytopenic, idiopathic [MeSH]</td>
<td>Infections [MeSH]</td>
</tr>
<tr>
<td>&quot;Idiopathic Thrombocytopenic&quot;</td>
<td>&quot;Infections&quot;</td>
</tr>
<tr>
<td>&quot;Immune Thrombocytopenia&quot;</td>
<td>Infection</td>
</tr>
<tr>
<td>&quot;immune thrombocytopenic purpura&quot;</td>
<td>Pneumonia [MeSH]</td>
</tr>
<tr>
<td>&quot;ITP&quot;</td>
<td>&quot;pneumonia&quot;</td>
</tr>
<tr>
<td>&quot;primary immune thrombocytopenia&quot;</td>
<td>Cystitis [MeSH]</td>
</tr>
<tr>
<td></td>
<td>&quot;Cystitis&quot;</td>
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<tr>
<td></td>
<td>&quot;urinary tract infection&quot;</td>
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<tr>
<td></td>
<td>Urinary Tract Infections [MeSH]</td>
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<tr>
<td></td>
<td>Sepsis [MeSH]</td>
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<td></td>
<td>&quot;Sepsis&quot;</td>
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<td></td>
<td>Bacteremia [MeSH]</td>
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<td>&quot;Bacteremia&quot;</td>
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<td></td>
<td>Erysipelas [MeSH]</td>
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<td>Encephalitis [MeSH]</td>
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<td></td>
<td>Respiratory Tract Diseases [MeSH]</td>
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<td></td>
<td>&quot;Respiratory Tract Diseases&quot;</td>
</tr>
</tbody>
</table>
Risk of infection in adult patients with Primary Immune Thrombocytopenia (ITP): A systematic review

Supplementary material

Quality analyses of the primary studies

The Newcastle-Ottawa Scale [36] was used for detecting bias in the primary studies [15,37,38]. The Newcastle Ottawa Scala is a quality assessment scale for observational studies. The scale contains 8 items with 3 categories: Selection (maximum: 4 stars), comparability (maximum: 2 stars) and outcome (maximum 3 stars). A maximum of 9 stars can be given. A high score indicates low risk of bias in the study. Each study was analyzed by the two investigators (EAP and MS). All 3 studies were assessed a high score (8 out of 9 stars) which indicated low risk of bias within the studies. All studies missed a star, because none of the studies demonstrated that the outcome of interest (infection) was not present at the start of study. Further comments can be found in the table below.

<table>
<thead>
<tr>
<th>Author Ref.</th>
<th>SELECTION (4 stars)</th>
<th>COMPARABILITY (2 stars)</th>
<th>OUTCOME (3 stars)</th>
<th>Adequacy of Follow-Up of Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nørgaard et al. (2011) [15]</td>
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<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
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<tr>
<td>Frederiksen et al. (2014) [37]</td>
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<td>Thomsen et al. (2009) [38]</td>
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<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
</tbody>
</table>

** Stars:
- Selection (max 4 stars), ** Comparability (max 2 stars), *** Outcome (max 3 stars)