1 **Infections due to Dysregulated Immunity: An emerging complication of**

2 **Cancer Immunotherapy**

3 Tommaso Morelli[1,2], Kohei Fujita [3], Gil Redelman-Sidi [4], Paul Elkington [1,2]

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5 [1] NIHR Biomedical Research Centre, School of Clinical and Experimental Sciences, Faculty of

6 Medicine, University of Southampton, Southampton, United Kingdom.

7 [2] Institute for Life Sciences, University of Southampton, Southampton, United Kingdom.

8 [3] Division of Respiratory Medicine, Centre for Respiratory Diseases, National Hospital Organization

9 Kyoto Medical Centre, Kyoto, Japan

10 [4] Division of Infectious Diseases, Memorial Sloan Kettering Cancer Centre, New York, USA

11

12 **Address for correspondence:**

13 Professor Paul Elkington

14 Clinical and Experimental Sciences

15 University of Southampton, Southampton SO16 1YD

16 Tel.:   00 44 23 8079 5928

17 E-mail: p.elkington@soton.ac.uk

Abstract

Immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment. However, immune related adverse events (irAEs) are a common side-effect, which can mimic infection. Additionally, treatment of irAEs with corticosteroids and other immunosuppressant agents can lead to opportunistic infection, which we have classed as ImmunoTherapy Infections due to ImmunoSuppression (ITI-IS). However, emerging reports demonstrate that some infections can be precipitated by ICIs in the absence of immunosuppressive treatment, in contrast to the majority of reported cases. These infections are characterised by a dysregulated inflammatory immune response, and so we propose they are described as ImmunoTherapy Infections due to Dysregulated Immunity (ITI-DI). This review summarises the rapidly emerging evidence of these phenomena and proposes a new framework for considering infection in the context of cancer immunotherapy.

Introduction

In 1957 Macfarlane Burnet wrote "The failure in cancer is due not to any weakness of the organism, but to a change in the character of the cells, rendering them in one way or another insusceptible to the normal control".[1] Subsequently, evading immune destruction was identified as a critical hallmark of cancer.[2] The 2018 Nobel prize was awarded to James Allison and Tasuku Honjo for the discovery that cancer cells could exploit programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4) signalling to avoid immune destruction.[3]

PD-1 is an immune checkpoint molecule expressed on effector T cells and binds to PD-L1 and PD-L2 on antigen presenting cells (APCs**).** Tumour cells can also express PD-L1 as a method of evading immune destruction, whereby PD-1/L1 signalling supresses effector T cell priming and proliferation. CTLA-4 is another co-inhibitory receptor expressed on effector T cells. CTLA-4 competes with the costimulatory receptor CD28 on effector T cells for binding with activation ligands CD80/86, found on APCs. CD28 binding to CD80/86 is essential for T cell receptor (TCR) signalling and hence CTLA-4, which binds to CD80/86 with greater affinity, effectively prevents effector T cell activation. CTLA-4 and PD-1 are expressed on effector T cells following chronic, sustained antigen exposure.[4-6]

PD-1 and CTLA-4 signalling thus acts as a "brake" to balance and prevent an over-exuberant damaging immune response, for example in chronic infection. PD-1/PD-L1 signalling can be inhibited using monoclonal antibodies against PD-1 (e.g. pembrolizumab, nivolumab) and PD-L1 (e.g. durvalumab, atezolizumab, avelumab). CTLA-4 signalling can similarly be blocked using monoclonal antibodies such as ipilimumab and tremelimumab. Immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment, with improved survival demonstrated in many forms of cancer, including lung cancer, melanoma, colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, bladder cancer, Merkel cell carcinoma and Hodgkin's lymphoma.[4] ICIs require close monitoring as they are associated with autoimmune phenomena known as immune related adverse events (irAEs).[4]

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Immune Related Adverse Events (irAEs)

58 IrAEs are a common side effect of ICIs, with an incidence between 54%-76% according to a

59 metanalysis of trial data.[7] IrAEs can affect any body system and management often involves

60 treatment with glucocorticoids such as prednisolone and other immunosuppression such as anti-TNF

61 therapy for steroid refractory cases. From the pulmonary perspective, immune related pneumonitis

62 occurs more commonly with PD-1 blockade and has several radiological presentations including

63 cryptogenic organising pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonitis,

64 acute interstitial pneumonia and pulmonary sarcoid reactions.[5] Combination ICI therapy appears to

65 increase the risk of irAEs.[8] The pathogenesis of irAEs may be mediated by T cell autoimmunity,

66 impaired regulatory T Cell (Treg) function, TH17 helper T cells and T cell mediated autoantibodies.[4]

67 Notably, irAEs can mimic infection.[9] Recently it has been hypothesised that immune checkpoint

68 blockade may cause increased immune recognition of commensal bacteria, such as gut microbiota,

69 perhaps via attenuated Treg function, and this immune recognition of commensal bacteria can cause

70 expansion of TH17 cells that have the potential to migrate and potentially cause irAEs.[10]

Consequences of Natural Immune Checkpoint Loss of Function

72 Immune checkpoints help prevent activity against self. Consequently, polymorphisms in CTLA-4 and

73 PD-1 are associated with autoimmune sequalae such as Addison's disease, coeliac disease, Graves'

74 disease, type 1 diabetes mellitus, myasthenia gravis, rheumatoid arthritis, and systemic lupus

75 erythematosus.[4][6]

76 In addition, genetic mutations in these receptors predict that pharmacological targeting of immune

77 checkpoints may have infectious complications. CHAI (CTLA-4 haploinsufficiency with autoimmune

78 sequelae) and LATAIE (LRBA deficiency with autoantibodies, regulatory T cell defects, autoimmune

79 infiltration and enteropathy) are human genetic disorders associated with deficient CTLA-4

80   expression and function. CHAI and LATAIE manifest with multiorgan lymphocytic infiltration, T_{reg}

81   defects and autoantibody production and are also associated with recurrent infections, particularly

82   respiratory infections.[11] A review of the phenotype of LATAIE patients revealed 71% suffered from

83   recurrent infections (upper respiratory tract, lower respiratory tract and urinary). Reported bacterial

84   infections included a range of pathogens, such as *Escherichia coli, Klebsiella pneumoniae,*

85   *Haemophilus influenzae, Pseudomonas aeruginosa, Campylobacter,* and *Staphylococcus aureus*.

86   Reported viral infections include *cytomegalovirus, adenovirus, norovirus,* and *varicella zoster*, and

87   candida infections are also described.[12] Although these genetically determined phenotypes have

88   more severe manifestations than CTLA-4 associated irAEs, they provide some insight into the natural

89   consequences of loss of CTLA-4 function. Interestingly CTLA-4 mutations have also been associated

90   with more severe tuberculosis infection in an African population study.[13] With Respect to PD-1/PD-

91   L1, although there are no human congenital diseases associated with deficiency, PD-1 deficient mice

92   are highly susceptible to tuberculosis infection.[14] [15]

93   Given the emerging evidence of increased infection in patients treated with ICIs, and evidence that

94   immune checkpoint deficiency can be associated with recurrent infections, we were interested in

95   evaluating the infectious sequelae of ICI therapy. Furthermore, we aimed to characterise the

96   pattern of these infectious complications to inform future clinical management strategies and the

97   associated research agenda.

98   **Literature Search**

99   We performed a literature search to identify reports of adult cancer patients who were found to

100 have developed infections after ICI initiation. The search protocol was registered on PROSPERO (CRD

101 4202141634, see Appendices 1-3). We searched Medline (Ovid 1996- February week 4 2021) using

102 advanced search, for the following keywords: ("Infection" or "Infectious Disease") and ("Immune

103 checkpoint inhibitor" or "PD-1" or "PD-L1" or "CTLA-4"). Additional limits were placed to include

104 articles relevant to humans and those published in the English language. This search yielded 1294

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105 results. Thirty-four additional relevant studies were identified through co-author suggestion,

106 references and citations. After screening for suitability by viewing the title, abstract, introduction

107 and conclusion, and removing duplicates, 95 full text articles were assessed. Seventy-nine studies

108 were included for analysis (Figure 1). Information on cancer type, ICI used, concurrent

109 immunosuppression and available descriptive statistics were collected. Table S1 summarises the

110 studies of immunotherapy associated infection.

111 **Prospective Randomised Clinical Trial Data**

112 Trial data has not demonstrated a significantly increased rate or risk of infection following ICI

113 treatment.[16] A review of Phase I trial data revealed infection-related adverse events in 18% of

114 patients and the odds ratio of infection was not statistically different from molecular targeted agents

115 for cancer.[17] One study of patients with non-small cell lung cancer (NSCLC) treated with

116 pembrolizumab reported complications of pneumonia (1.5%), lung infection (0.3%), oral candidiasis

117 (0.3%) and urinary tract infection (0.3%).[18] Another RCT reported a case of pneumonia and severe

118 *Varicella zoster* infection following nivolumab for NSCLC.[19] Eight cases of drug related infection,

119 including one severe *Varicella zoster* infection, were reported in a nivolumab trial for melanoma.[20]

120 Sepsis following atezolizumab for bladder cancer has also been reported.[21] However, while RCTs are

121 the gold standard for determining treatment efficacy by minimising bias, they do not adequately

122 assess all potential treatment harms, especially if infrequent.[22] Typically these only come to light in

123 post-marketing surveillance when greater numbers of patients are treated.[23] Additionally whilst the

124 total reported infections is small, there may be underreporting in trials as causality to ICIs is not

125 clearly established. Thus, analysis of other forms of data such as clinical observational data is

126 required.

127 **Opportunistic Infections associated with irAE treatment**

128   The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provided a

129   consensus statement which suggested that ICIs do not intrinsically increase the risk of infection, but

130   rather immunosuppressive therapy to treat irAEs can predispose to opportunistic infection.[16] This

131   followed a retrospective cohort review from Del Castillo et al who analysed records 740 melanoma

132   patients who received ICIs over a four year period and recorded the number of infections requiring

133   hospitalisation or anti-microbial treatment.[24] Seven percent of patients developed infection and

134   17% of these patients died. The vast majority (73.2%) of patients received CTLA-4 blockade with

135   ipilimumab, 14.9% had PD-1 blockade, while 11.7% had combination ICI therapy. Eighty-five percent

136   of infections were bacterial with 13/23 being pneumonia. Two cases of invasive pulmonary

137   aspergillosis, three *Pneumocystis jirovecii* pneumonia, one candidemia and one strongyloidiasis case

138   were reported. Risk factors for infection included corticosteroid administration (OR 7.71 p <0.0001),

139   infliximab (OR 4.74 p<0.0001) and combined PD-1/CTLA-4 blockade (OR 3.26 p 0.0017).[24]

140   There are multiple case reports which have also highlighted multiple instances of opportunistic

141   infection following irAE immunosuppression with a variety of causative pathogens including

142   *Aspergillus fumigatus,*[25-28] *Pneumocystis jirovecii,*[29-31] *JC virus,*[32], *Cytomegalovirus*[33] and

143   *Campylobacter*[34] (Summarised in Table 1). These reports highlight the need to have a low threshold

144   of investigation for opportunistic infection following irAE treatment and consideration of

145   *Pneumocystis jirovecii* prophylaxis. In addition to prior immunosuppressive cancer treatments,

146   comorbidities such as COPD in lung cancer patients and the immunosuppressive tumour

147   microenvironment are risk factors for infections[35 36].

148   **ICI-associated infection independent of immunosuppression**

149   Whilst the predominant infection risk post ICI treatment is likely to be due to immunosuppression,

150   there is mounting evidence of a second mechanism that leads to increased incidence of infection.

151   For example, Fujita et al reviewed 167 records of patients who received nivolumab for non-small cell

152 lung cancer and 19.2% (32 patients) were treated for infection.[37] There were 33 infections, 78.1%

153 were bacterial and included *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella*

154 *pneumoniae,* methicillin resistant *Staphylococcus aureus (MRSA),* methicillin sensitive

155 *Staphylococcus aureus (MSSA), Staphylococcus schleiferi*, *Mycobacterium tuberculosis* and other

156 unknown presumed bacterial infection. 6.3% were fungal and included *Aspergillus fumigatus* and

157 *Candida albicans* infection, while 18.8% were viral and included *Varicella* and *Influenza*. Diabetes

158 significantly increased the risk of infection (OR 3.61 p =0.028).[37] Of note, this study exclusively

159 analysed PD-1 blockade in the form of nivolumab. Unlike the Del Castillo study, there was no

160 significant difference in the number of infections with use of corticosteroids or other

161 immunosuppressive agents, suggesting an alternative mechanism.

162 Kanjanapan and Yip recently published a cohort study of 327 patients with primarily NSCLC (36%)

163 and melanoma (47%).[38] The majority (77%) of patients received PD-1/PD-L1 therapy, 9% received

164 CTLA-4 therapy, and 14% received combination therapy. The rate of infection up to 12 months post

165 immunotherapy was 27%, age was the only identified risk factor for infections post ICI initiation (HR

166 1.73 p= 0.04), while corticosteroid use and diabetes mellitus were not risk factors for post ICI

167 infection. The rate of infection in the pre-ICI period was 34%, but notably infectious episodes were

168 defined through positive culture or polymerase chain reaction potentially allowing inclusion of

169 commensal colonisation such as *Staphylococcus aureus* on the skin (55 identified in the pre-ICI

170 period and defined as infection). Furthermore, given the long study period of 7 years it is not

171 possible to directly compare the rates of infection pre and post ICI. However, there was still a

172 significant number of infections in the post ICI period and corticosteroids were not a statistically

173 significant risk factor.[38]

174 Furthermore, a recent study retrospectively evaluated infectious sequelae in 200 patients in a

175 French registry, treated with PD-1 (98.5%), and PD-L1 inhibitors (1.5%). 60% of patients had

176 melanoma, 35.5% had NSCLC.[39] Infection occurred in 18% between 19 and 132 days after ICI

177   initiation, of which 58.3% were suspected pulmonary infection which improved with antibiotics,

178   19.4% were skin infections, 19.4% urinary tract infections and 2.9% GI infection. There were no

179   cases of *Pneumocystis jirovecii* or other typical opportunistic infections. No association with

180   corticosteroids, or other immunosuppressant medication, was reported in this study, again

181   suggesting that immunosuppression was not the primary driver.[39]

182   These more recent studies together suggest that other factors other than corticosteroids and

183   immunosuppression may play a role in post ICI infection. There are diverse reports of infection, in

184   which it appears the hyper-inflammatory dysregulated immunity associated with ICIs drives

185   pathogenesis. We propose these can be characterised as ImmunoTherapy Infections due to

186   Dysregulated Immunity (ITI-DI), to distinguish them from ImmunoTherapy Infections due to

187   ImmunoSuppression (ITI-IS). ITI-DI may be considered an entirely different pathological mechanism,

188   whereby the excessive host immune response due to inhibition of immune checkpoints counter-

189   intuitively favours the pathogen (Figure 2).

190   **Emerging examples of ImmunoTherapy Infections due to Dysregulated Immunity (ITI-DI)**

191   *Mycobacterium tuberculosis* **and atypical mycobacterial infection**

192   Tuberculosis reactivation was one of the first ICI-associated infections to be described. Currently

193   there are at least nineteen case reports of *Mycobacterium tuberculosis* (Mtb) reactivation following

194   PD-1/PD-L1 blockade[40-55] (Figure 3 and Table S1). A review of the US Food and Drug Administration

195   Adverse Events Reporting (FAERS) system for the incidence of Mtb revealed 72 cases of Mtb

196   following PD-1/PD-L1 blockade. The reporting odds ratio for Mtb infection with PD-1/PD-L1

197   inhibitors was 1.79 (95% CI, 1.42 to 2.26) (p<0.0001),[56] demonstrating increased risk of active TB. In

198   addition, due to the clinical similarity in features of cancer progression and mycobacterial infection,

199   it seems likely that cases are underreported through underdiagnosis.[55] Similarly, analysis of a single

200   centre cohort of 297 patients in Japan with lung cancer receiving treatment with pembrolizumab,

201   nivolumab, atezolizumab or durvalumab revealed an incidence of Mtb reactivation of 1.7%

202 developing 22-398 days after initiation of ICI treatment.[57] This is higher than the incidence of Mtb

203 reactivation in lung cancer reported in the 1980s, when generally higher doses of cytotoxic

204 chemotherapy were used.[58] Also, a single centre cohort in South Korea identified 3 cases of Mtb,

205 and calculated an incidence rate of 394.4 per 100, 000 person years, higher than the rate in the

206 South Korean population in 2018 and previous studies that included patients with lung cancer.[59]

207 Finally, a single centre cohort in Singapore showed that 4/191 (2.09%) of patients developed Mtb

208 reactivation following PD-1/PD-L1 blockade.[60]

209 Atypical mycobacterial infection (AMI) has also been associated with immunotherapy. We found

210 four cases of atypical mycobacterium infection following PD-1/PD-L1 immunotherapy in the absence

211 of immunosuppression.[61 62] Analysis of the FAERS database revealed thirteen cases of AMI following

212 PD-1/L1 blockade, similarly suggesting elevated risk of infection. The reporting odds ratio for AMI

213 was 5.49 (CI, 3.15 to 9.55 p<0.0001).[56]

214 In terms of the underlying mechanism, transgenic murine studies have demonstrated that PD-1

215 knockout mice had increased susceptibility to Mtb infection, succumbing even more rapidly than

216 IFN-γ deficient mice [14 15] . In a human 3D cell culture system, PD-1 blockade leads to excessive

217 cytokine secretion, and TNF-α may play a central role [63]. Similarly, TB infected macaques given anti-

218 PD-1 antibodies develop worse disease, have higher bacterial loads as well as elevation of multiple

219 inflammatory cytokines, compared to non-PD-1 treated macaques. [64] Notably these studies suggest

220 PD-1 blockade negatively affects host-Mtb interaction even in the absence of any

221 immunosuppression, favouring pathogen proliferation over host control due to a dysregulated

222 immune response.

223 These emerging clinical observations, animal modelling and advanced cell culture modelling studies

224 all suggest that disruption of the PD-1/PD-L1 axis results in hyper-inflammatory conditions that

225 favour mycobacterial growth. Consequently, diverse groups have suggested all patients should have

226 interferon γ release assay (IGRA) testing prior to ICI initiation and there may be merit in serial IGRA

227   testing before starting immunosuppressive therapies for irAEs.[43 65 66] The evidence presented here

228   further supports screening of patients for latent Mtb before starting anti-PD-1 treatment and

229   investigation for mycobacterial infection when clinical features are suggestive, especially in high

230   incidence settings. Notably to date, reports of TB primarily centre on the PD-1/PD-L1 axis and there

231   are no cases of CTLA-4 inhibitor monotherapy causing Mtb reactivation.

232   **Hepatitis B Virus**

233   Hepatitis B infected patients were excluded from the initial immunotherapy RCTs. Subsequently,

234   there are multiple reports of hepatitis B reactivation, including cases where immunosuppression has

235   been absent.[67-71] Furthermore, Burns et al analysed the FAERS database for reported cases of

236   hepatitis B and determined the reporting odds ratio for reactivation with pembrolizumab to be 2.32

237   (95% CI 1.11-4.28 p=0.013)[72], thus highlighting elevated risk of viral reactivation with

238   pembrolizumab. Consistent with this, in a retrospective cohort study of 114 cancer patients with a

239   history of hepatitis B who received ICIs, 5.3% developed reactivation of hepatitis B virus.[71] All six

240   patients had undetectable viral DNA at baseline and received PD-1/PD-L1 blockade. Absence of

241   antiviral prophylaxis was the only significant risk factor (OR 17.50 1.95-157.07 p= 0.004). Notably,

242   12.7% were on concurrent corticosteroids, which were not a significant risk factor, suggesting ICI

243   treatment may have been causative.[71] Additionally, a systematic review of patients with hepatitis B

244   or C revealed that, although ICIs were generally safe, 2.8% showed an increase viral load among 106

245   patients not on antiviral treatment.[73]   Furthermore, Lee et al retrospectively reviewed records of 62

246   patients with hepatitis B related hepatocellular carcinoma. Of the six patients who did not receive

247   antiviral treatment, one developed reactivation of hepatitis B after being treated with nivolumab,

248   while none of the patients who received antiviral therapy developed reactivation of hepatitis B

249   suggesting this may prevent reactivation with ICI.[74] Notably, viral titres do not appear to be

250   monitored routinely in all centres. One review identified that only six out of 35 patients with

251   hepatitis B/C infection had pre and post treatment viral titres available and did not identify any

252   reactivation, though it is unclear if these patients were on antiviral therapy.[75] Another retrospective

253   analysis of nineteen patients with a history of hepatitis B/C revealed only seven patients had viral

254   titre measurement after starting ICI treatment.[76]

255   Whilst Hepatitis B after ICI treatment can be associated with immunosuppression states,[69] there is

256   emerging evidence that excess inflammation can also promote viral replication. Immunological

257   assays of chronic hepatitis B virus infected patients have associated high concentrations of PD-1

258   expressing cytotoxic T lymphocytes with a reduction in acute flares of hepatitis B, while lower

259   number of PD-1 expressing lymphocytes had a higher number of acute flares.[77] Furthermore, PD-1

260   expressing lymphocytes were also shown to be functional and secrete interferon-γ, challenging an

261   assumption that these cells are "exhausted".[77] Excess cytokine release by blocking PD-1/PD-L1 may

262   result in destruction of hepatocytes, allowing escape of infectious, previously latent virus.[78]

263   Thus, PD-1 expressing lymphocytes appear to assist with viral control, while blockade of PD-1/PD-L1

264   signalling and the resulting hyper-inflammatory state may disrupt balanced immune control

265   established in latent hepatitis B infection and promote viral growth. Whilst immunotherapy may be

266   used safely in chronic hepatitis B infection, there is a subset of patients who may develop viral

267   reactivation. Hence appropriate screening and monitoring of hepatitis virus status is vital.

268   **Human Herpesviridae: cytomegalovirus, varicella zoster virus, Epstein-Barr virus**

269   *Cytomegalovirus (CMV), Epstein-Barr virus (EBV)* and *Varicella-zoster virus (VZV)* are herpesviruses

270   that establish a state of chronic latent infection in most humans by adulthood.[79] Whilst there are a

271   number of reports of CMV following immunosuppression[33 80 81], reactivation of CMV[82 83], EBV[84] and

272   VZV[85 86] in the absence of immunosuppression has also been reported, with features mimicking

273   irAEs.[87] In fact, some evidence suggests CMV may actually be an underlying trigger for severe irAEs,

274   as CMV is found disproportionately among severe ICI-associated pneumonitis and colitis.[88 89] A

275   retrospective cohort study analysing checkpoint inhibitor pneumonitis (CIP) revealed that CMV pp65

276   positivity rate in severe CIP patients was much higher than that in patients without or with mild ICI-

277 pneumonitis (91.7 vs 20%).[88] A cohort study by Franklin et al revealed that CMV reactivation was

278 present in all treatment refractory cases through detection of CMV-DNA in biopsy or plasma, or

279 CMV IgM. [89]

280 Whilst immunosuppression could be the causative factor in some reported cases, the hyper-

281 inflammatory state can promote viral pathology. For example in inflammatory bowel disease, colonic

282 inflammation can impair natural killer cell function, and this along with a damaged mucosa from

283 immunopathology can promote viral reactivation.[90] This suggests a potential role for dysregulated

284 inflammation in a subset of ICI-associated CMV infection. ICIs may boost virus-specific T cell specific

285 activity,[91] and then inflammation driven by IL-6 and IL-17 may enhance viral persistence by

286 protecting virus-infected cells from apoptosis through expression of Bcl-2 and Bcl-xL[92] [93].

287 Additionally, in macaques CTLA-4/PD-1 blockade can cause reactivation of SIV.[94] Overall, these

288 reports argue for a low threshold for investigating for herpesvirus infection before starting

289 immunosuppression for potential irAEs.

290 **Fungal infections**

291 Whilst fungal infection can be a direct consequence of immunosuppression, an emerging number of

292 cases of progressive fungal infection exacerbated by immunotherapy in the absence of

293 immunosuppression are being reported, such as aspergillosis (Figure 4). [95] Dysregulated immunity

294 appears to play a role, indicated by dramatic worsening of chronic progressive pulmonary

295 aspergillosis and fulminant deterioration of nasal fungal sinusitis post immunotherapy. Again, clinical

296 presentation can mimic cancer progression, with pulmonary cavitation[95 96], erosive skull base lesions

297 with bilateral cavernous sinus involvement[97] and new pulmonary nodules with pleural effusion,[98 98]

298 and so cases may well be under-reported. In these situations, immune checkpoint blockade may

299 cause an exaggerated immune response to fungal colonisation, which could promote fungal growth

300 similar to recent studies in Mtb infection. [64]

301

302 *Clostridium difficile*

303 Babacan et al reported 5 cases of *Clostridium difficile* infection (CDI) and irAE colitis, and

304 interestingly 4 of the cases did not have prior exposure to antibiotics and the other case did not have

305 any immunosuppressive treatment.[99] Additionally, CDI preceding irAE colitis has been reported.[100][101]

306 Inflammatory bowel disease can present with CDI, even in the absence of immunosuppression, [102]

307 suggesting that excessive inflammation can favour CDI. Given similar pathophysiology in IBD and

308 irAE colitis,[103] there may be a subset of patients that develop CDI because of the acquired hyper-

309 inflammatory state. Evolving evidence demonstrates that ICIs can alter the gut microbiota, and CDI

310 may be a manifestation of this.[104]

311 **Severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2)**

312 In addition to reactivating chronic infections, ICI therapy may worsen acute infections associated

313 with immune asynchrony such as SARS-CoV-2. Cancer patients may have higher risks of severe

314 complications outcomes with SARS-CoV-2 infection regardless of ICI therapy.[105] Interestingly, cancer

315 patients may also have a poor vaccine response, with reduced immunogenicity post a single dose of

316 vaccine.[106] Furthermore, patients with haematological malignancies in particular are at risk of

317 reduced seroconversion, prolonged viral shedding, and sustained immune dysregulation following

318 SARS-CoV-2 infection.[107] These factors make analysis challenging. However, some reports describe

319 rapidly progressive SARS-Co-V-2 following ICIs.[108][109] In a retrospective analysis of 423 cases of cancer

320 patients diagnosed with SARS-CoV-2, ICI use was an independent risk factor for hospitalisation

321 (univariate analysis odds ratio 2.53, 1.18-5.67, p=0.017, multivariate analysis odds ratio 2.84, 1.24-

322 6.72, p= 0.013) and requirement for high flow oxygen support or mechanical ventilation (univariate

323 analysis hazard ratio 2.38, 1.29-4.38, p= 0.005, multivariate analysis hazard ratio 2.38, 1.29-4.38, p=

324 0.004).[110] The risk was different in lung cancer compared to other solid cancers. For lung cancer,

325 12/23 (52%) patients not on ICIs were hospitalised, 35% developed severe respiratory illness,

326 compared to 10/12 (83%) of lung cancer patients on ICIs, of whom 58% developed severe

327   respiratory illness. Interestingly only one of 31 ICI-treated patients received corticosteroid therapy

328   prior to SARS-Co-V-2 diagnosis. In contrast, systemic chemotherapy within 30 days was not a risk

329   factor for hospitalisation or severity of illness in this study.[110] Another Italian cohort study identified

330   that ICI as well as chemotherapy increased the risk of hospitalisation and death due to SARS-Co-V-

331   2.[111] Therefore, these series support an adverse interaction between ICIs and SARS-CoV-2 infection,

332   although other studies have not replicated these findings.[112-115] Additionally, it has been suggested

333   lung injury induced by SARS Co-V-2 may increase the risk of subsequent irAE pneumonitis.[116]

334   In terms of the underlying mechanism, ICI induced immune asynchrony is a potential explanation for

335   more severe COVID-19 infection. Patients with SARS-Co-V-2 infection who are admitted to ICU have

336   higher plasma concentrations of IL-2, IL-6, IL-7, IL-10 and TNF-α and severe SARS-CoV-2 is associated

337   with a cytokine storm.[117-119] Of note, high concentrations of inflammatory cytokines have predictive

338   potential in irAEs and can also correlate with irAE severity in PD-1 immunotherapy.[120] Additionally,

339   cytokine release syndrome is a rare complication of PD-1 immunotherapy.[121]   Taken together, ICIs

340   could promote a cytokine storm in SARS-CoV-2 via immune dysregulation, increasing the risk of a

341   harmfully excessive response to the pathogen. Recent observations such as the potential benefits of

342   Tocilizumab, an anti IL-6 agent[122], supports the hypothesis that severe COVID-19 infection is

343   exacerbated by an asynchronous, dysregulated immune state. Clinically it is important to distinguish

344   between SARS-Co-V-2infection and irAE pneumonitis in patients on ICIs.[123]

345   **Conclusion**

346   ICIs are transformative drugs that improve survival in many forms of cancer, but a common side

347   effect of immunotherapy is immune related adverse events. These irAEs are treated with

348   immunosuppression, which can cause opportunistic infection. However, an emerging paradigm is

349   that ICIs can also lead to a new pattern of infections resulting from dysregulated immunity, which

350   we term Immunotherapy Infections due to Dysregulated Immunity (ITI-DI). Immune checkpoint

351   activity may be necessary for the establishment of latent infection and a stable symbiosis between

352   pathogen and host, and so neutralising these with ICIs may in fact increase infection-related

353   immunopathology (Figure 5).[124] Screening for chronic infection such as latent TB and hepatitis should

354   be considered before starting ICI therapy, and infection reactivation should be considered within the

355   differential diagnosis even in the absence of immunosuppression.

356

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733

734 **Table 1: ImmunoTherapy Infections due to ImmunoSuppression (ITI-IS)**

735

Authors	Study Types	ICI class	Immunosuppressive Agents	Pathogen
(Arriola, Wheater et al. 2015, Del Castillo, Romero et al. 2016, Schwarz, Kocher et al. 2019, Liu, Liu et al. 2020, Si, Erickson et al. 2020)	Case report, Cohort	CTLA-4, PD-1, PD-L1	Corticosteroids, TNF-α antagonists, Mycophenolate mofetil	*Pneumocystis jirovecii*
(Lord, Hackman et al. 2010, Kyi, Hellmann et al. 2014, Del Castillo, Romero et al. 2016, Gupta, Tun et al. 2019, Oltolini, Ripa et al. 2019, Liu, Liu et al. 2020, Malek, Taremi et al. 2020, Taima, Tanaka et al. 2020)	Case report, cohort	CTLA-4, PD-1, PD-L1	Corticosteroids, TNF-α antagonists, Rituximab, Mycophenolate Mofetil, Tacrolimus, Rapamycin	*Aspergillus fumigatus*
(Del Castillo, Romero et al. 2016, Liu, Liu et al. 2020)	Case report, Cohort	CTLA-4, PD-1, PD-L1	Corticosteroids, TNF-α antagonists	*Candida albicans*
(Uslu, Agaimy et al. 2015, Del Castillo, Romero et al. 2016, Oltolini, Ripa et al. 2019, Schwarz, Kocher et al. 2019, Liu, Liu et al. 2020)	Case report, Cohort	CTLA-4, PD-1	Corticosteroids, TNF-α antagonists, Mycophenolate mofetil	*Cytomegalovirus*
(Martinot, Ahle et al. 2018)	Case report, unpublished pharmacovigilance registry data (WHO and Eudra-Vigilance)	CTLA-4 (PD-1 registry data)	Corticosteroids	*JC polyoma virus*
(Del Castillo, Romero et al. 2016, Oltolini, Ripa et al. 2019, Lee, Shaw et al. 2020, Liu, Liu et al. 2020)	Case report, Cohort	CTLA-4, PD-1, PD-L1	Corticosteroids, TNF-α antagonists	Other bacterial: including non specified organism, bacteraemic sepsis , *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Corynebacterium striatu, Campylobacter*

736

Figure legends

Figure 1: PRISMA chart

Figure 2: Spectrum of Immunotherapy associated infections. Whilst immunosuppression alone can cause infectious complications, the dysregulated immunity that results from immune checkpoint inhibition can lead to different patterns of infection reactivation due to excessive inflammation, thereby resulting in a spectrum of disease phenotypes.

Figure 3: Development of pulmonary TB on Triplet chemotherapy. Comparison of diagnostic CT scan performed 2 weeks before treatment (A) with the CT scan at time of TB diagnosis (B) shows regression of the tumour with immune checkpoint inhibition but new consolidation with cavitation.

Figure 4: Development of pulmonary aspergillus infection on nivolumab treatment. Original publication: Inthasot et al (2020) *Acta Clinica Belgica*, 75:4, 308-310, Reproduced with permission of publisher.

Figure 5: Potential Mechanisms whereby ICIs may lead to reactivation of infection and immune-related tissue damage. Sustained antigen exposure from persistently infected cells can cause an over-exuberant immune response harmful to the host. Immune Checkpoints (IC) may regulate homeostasis in latent infection, while signalling disruption with ICIs may promote excessive inflammation, infection reactivation and immunopathology.

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching
(n = 1294)

Records identified through co authors, references, citations
(n =34)

Screening

Records after duplicates removed
(n = 1290)

Records screened
(n =1290)

Records excluded
(n =1195)

Eligibility

Full-text articles assessed for eligibility
(n =95)

Full-text articles excluded,
(n = 16)

Included

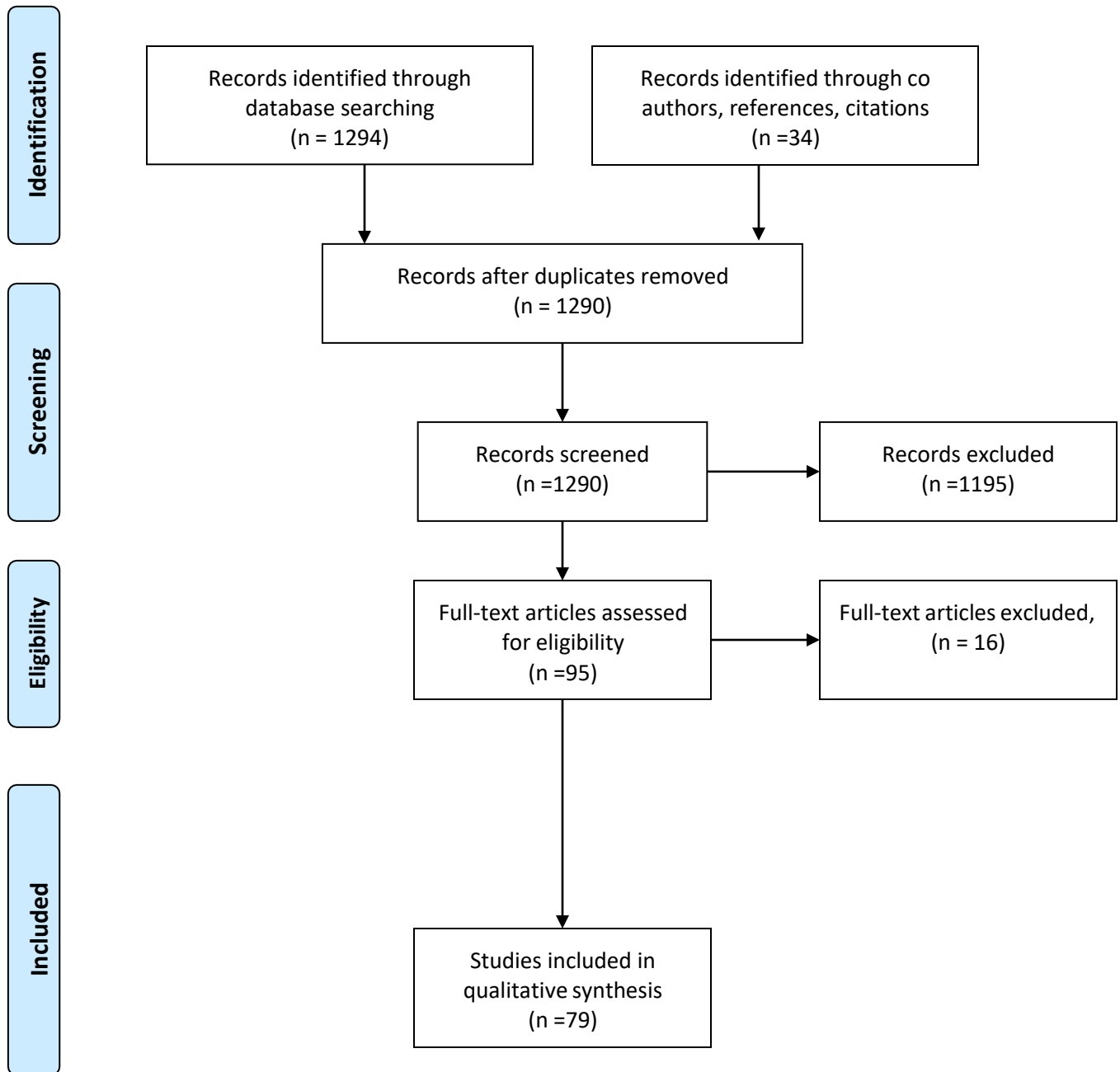Studies included in qualitative synthesis
(n =79)

Figure 1: PRISMA chart

Immunosuppression
ITI-IS

Dysregulated immunity
ITI-DI

Aspergillus

Pneumococcus

C diff

CMV

JC virus

HBV

PCP

Mtb

T Cell

PD-1

PD-L1

Tolerogenic
Signalling

atent Infection

Persistently
Infected Cell

IC
Inhibition

Excessiv
Inflammat

e.g. TNF
IL-6
IL-17
Cytotoxic

Immunopathology
Pathogen release and prolife
Active Infection