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Review article

Determinants of bacterial survival and proliferation in blood

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One sentence summary

This review provides an overview of the key factors evolved by bacteria to subvert immune defenses triggered by bloodstream infection, highlighting a combination of specific and universal molecular mechanisms that could be targeted by future therapies.

24 **Abstract**

25 Bloodstream infection is a major public health concern associated with high mortality and high
26 healthcare costs worldwide. Bacteremia can trigger fatal sepsis whose prevention, diagnosis
27 and management have been recognized as a global health priority by the World Health
28 Organization. Additionally, infection control is increasingly threatened by antimicrobial
29 resistance, which is the focus of global action plans in the framework of a One Health response.
30 In-depth knowledge of the infection process is needed to develop efficient preventive and
31 therapeutic measures. The pathogenesis of bloodstream infection is a dynamic process
32 resulting from the invasion of the vascular system by bacteria, which finely regulate their
33 metabolic pathways and virulence factors to overcome the blood immune defenses and
34 proliferate. In this review, we highlight our current understanding of determinants of bacterial
35 survival and proliferation in the bloodstream and discuss their interactions with the molecular
36 and cellular components of blood.

37
38 **Keywords**

39 Bloodstream infection; bacteremia; bacterial pathogenesis; virulence factors; immune
40 subversion

41 Introduction

42 Bacteremia is the presence of viable bacteria in the bloodstream. It sometimes results
43 from activities such as toothbrushing, dental extraction or other minor medical procedures,
44 which generally lead to transient and asymptomatic colonization of the blood before bacterial
45 elimination by the immune system (Lockhart *et al.* 2008). On the other hand, it can constitute
46 a *bona fide* step of bacterial pathogenesis. Bacteria can enter the bloodstream directly from
47 a breach in the vascular system upon catheterization, surgery, intravenous drug injection,
48 arthropod bite, animal bite and scratches, or injuries such as accidents, falls and cuts. Blood
49 can also be colonized as a complication of a primary infection site, *e.g.*, following pneumonia,
50 meningitis, peritonitis, or skin, soft tissue, bone, joints, biliary or urinary tract infections.
51 Bacteria can then colonize other organs by hematogenous spread, triggering secondary
52 infections such as infectious endocarditis or osteomyelitis. Uncontrolled bloodstream
53 infections can ultimately lead to sepsis, septic shock and death (Hotchkiss *et al.* 2016).

54 Bloodstream infection is a major public health issue worldwide. Sepsis is estimated to
55 affect 31.5 million individuals leading to 5.3 million deaths annually, and its control has been
56 declared a health priority by the WHO (Fleischmann *et al.* 2016; Hotchkiss *et al.* 2016;
57 Reinhart *et al.* 2017). The incidence rate of bloodstream infections has been estimated to
58 range from 113 to 204 per 100,000 person-years in North America and Europe (Goto and Al-
59 Hasan 2013). In the same population, short-term fatality rates and mortality rates were 13-
60 20% and 20-37% per 100,000 person-years, respectively (Goto and Al-Hasan 2013). The
61 bacteria the most frequently isolated from blood are *Staphylococcus aureus* and *Escherichia*
62 *coli*. A worldwide sentinel study from 1997 to 2016 highlights inverse frequency trends with
63 *S. aureus* decreasing from 22 to 18%, while *E. coli* rising from 18 to 24% (Diekema *et al.*
64 2019). Urinary tract infection is the leading source of *E. coli* bloodstream infection. A recent
65 systematic review of the literature indicates an estimated incidence rate of *E. coli* bacteremia
66 reaching 48 per 100,000 person-years in high-income countries (Bonten *et al.* 2021). This
67 rate increases over 100 in 55- to 75-year-olds and over 300 in 75- to 85-year-olds. The

68 average estimated fatality rate of *E. coli* bacteremia is 12% (Bonten *et al.* 2021). Skin infection
69 is the most common cause of *S. aureus* bloodstream infection, which is associated with high
70 morbidity and mortality (Barnett *et al.* 2013; Stewardson *et al.* 2016). Far less frequent
71 bacteria responsible for bloodstream infections are *Klebsiella pneumoniae*, *Pseudomonas*
72 *aeruginosa*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Enterobacter cloacae*,
73 *Streptococcus pneumoniae*, *Enterococcus faecium* and *Acinetobacter baumannii*,
74 representing 2 to 7% (Diekema *et al.* 2019). In low-resource regions, *Salmonella enterica* is
75 a major cause of bloodstream infections (Reddy, Shaw and Crump 2010; Deen *et al.* 2012).

76 Bloodstream infections are associated with high mortality, long hospital stays and high
77 healthcare costs, especially those acquired by critically ill patients in intensive care units
78 (Naber 2009; Brunelli *et al.* 2016; Wang *et al.* 2020). The emergence and spread of multidrug-
79 resistant clones are additional concerns that limit therapeutic options and increase the
80 economic burden of bacteremia management. The prevalence of antibiotic-resistant
81 enterobacteria isolated from bloodstream infections has more than doubled in 20 years,
82 reaching 15,8% in 2016 (Diekema *et al.* 2019). In contrast, global prevalence of oxacilline-
83 resistant *S. aureus* slightly decreased among both hospital- and community-acquired isolates
84 (Diekema *et al.* 2019). Although bloodstream infections due to antibiotic-resistant bacteria
85 currently represent a minority of cases, they can cause a higher fatality and mortality risks
86 and a heavier economic burden per infection than susceptible isolates (Stewardson *et al.*
87 2016; Hattori *et al.* 2018; Kern and Rieg 2020; MacKinnon *et al.* 2021). Beyond the high
88 hospital costs associated with bloodstream infection care, long-term disabilities following
89 severe sepsis have major socioeconomic impacts (Iwashyna *et al.* 2010).

90 The pathogenesis of bloodstream infection is a complex and dynamic process. In broad
91 outline, it can be divided into several steps, starting with the invasion of the vascular system
92 by bacteria, possibly after tissue colonization and dissemination from a primary site of
93 infection, followed by interactions with blood immune components, potentially triggering
94 sepsis. In some cases, it can be followed by metastatic spread to secondary sites of infection.
95 Successful bloodstream infection relies on the capacity of bacteria to overcome host immune

96 defenses based on tissular barriers, liver and spleen clearance, immune cells, soluble
97 messengers and antibacterial factors. Invading bacteria face phagocytosis by neutrophils,
98 monocytes and macrophages. Killing occurs by the generation of toxic levels of reactive
99 oxygen and nitrogen species, fine-tuning of the homeostasis of metal nutrients, and the
100 production of antimicrobial peptides and proteases (Nathan 2006; Sheldon and Skaar 2019).
101 In blood, complement kills bacteria directly by forming the lytic membrane attack complex and
102 indirectly by mediating macrophage osponophagocytosis (Ricklin *et al.* 2010). Other
103 antibacterial defense components of the blood include platelet microbicidal proteins (PMPs)
104 and kinocidins released by alpha granules, interleukin 26, defensins and nutritional immunity
105 proteins such as transferrin, hemopexin and haptoglobin (Hood and Skaar 2012; Yeaman
106 2014; Larochette *et al.* 2019).

107 Several reviews have explored various stages of bloodstream infections, including
108 bacterial adhesion, invasion, crossing of host barriers, vascular invasion, bacterial survival in
109 blood or serum and dissemination (Lemichez *et al.* 2010; Miajlovic and Smith 2014; Abreu
110 and Barbosa 2017; Coureuil *et al.*, 2017; Le Guennec *et al.* 2020; Holmes *et al.* 2021).
111 However, these reviews focused on specific bacteria or specific barriers. Here, we propose a
112 broader perspective by examining the molecular mechanisms evolved by a wide range of
113 clinically relevant bacteria to resist host defenses and thrive in the bloodstream. This review
114 will encompass established survival mechanisms like complement and antimicrobial peptide
115 resistance, blood immune cell manipulation and subversion of nutritional immunity as well as
116 how bacteria regulate these regulatory processes. It will not consider how bacteria enter the
117 bloodstream and how they reach secondary sites of infection, due to the multiplicity of
118 mechanisms and diversity of contexts. We will focus on bacterial determinants of viability that
119 have been functionally validated in blood *ex vivo* and in animal models. Additionally, we
120 provide an in-depth analysis of over 40 genome-wide studies to shed light on metabolic
121 adaptations that enable bacterial survival and proliferation in blood. All in all, our review will
122 explore the critical factors that empower some bacteria to flourish in blood and distinguish
123 them from those that do not.

124 **Complement inhibitors**

125 The complement system (see Box 1) is one of the most important components of innate
126 immune response. It mediates host defense and homeostasis in plasma, at infection sites
127 and in intracellular space of some cell types. Complement deficiencies increase the risk for
128 invasive bacterial infection. Complement resistance is a critical property shared by bacteria
129 responsible for bloodstream infection, which developed mechanisms targeting virtually all
130 complement components to interfere with the complement cascade. The following section
131 highlights the key complement resistance factors expressed by bacteria that successfully
132 survive in the bloodstream. Bacterial factors targeting components common to the classical
133 pathway (CP), the lectin pathway (LP) and the alternative pathway (AP), such as C3 and C5,
134 are illustrated in the Figure 2. Bacterial factors targeting components of the CP/LP, AP or TP
135 are illustrated Figures 3, 4 and 5, respectively. Additionally, an extensive view of established
136 bacterial factors evolved to resist complement is presented in Supplementary Tables 1-4. For
137 a comprehensive panorama, the reader is referred to reviews considering general evasion
138 mechanisms (Zipfel et al. 2007; Lambris et al. 2008; Hovingh et al. 2016; Ermert et al. 2019;
139 Holmes *et al.* 2021) or focusing on factors expressed by specific bacteria, such as *E. coli*
140 (Miajlovic and Smith 2014; Abreu and Barbosa 2017), *S. aureus* (Pietrocola *et al.* 2017), *K.*
141 *pneumoniae* (Doorduyn *et al.* 2016), *P. aeruginosa* (González-Alsina *et al.* 2023), *Borrelia*
142 *burgdorferi* (Dulipati *et al.* 2020), *Haemophilus influenzae* and *Moraxella catarrhalis*
143 (Riesbeck 2020), *Leptospira* spp. (Barbosa and Isaac 2018), *Neisseria* spp. (Schneider *et al.*
144 2007; Lewis and Ram 2020), *Salmonella* and *Yersinia* spp. (Krukonis and Thomson 2020),
145 or *Streptococcus* spp. (Laabei and Ermert 2019; Syed *et al.* 2020).

146

147 **Inhibition of complement activation**

148 *S. aureus*, the most prominent bloodstream infection-associated Gram-positive
149 bacterium, is exceptionally well equipped with surface components and secreted effectors
150 that disrupt complement pathways at virtually every step of the cascade. Like other Gram-

151 positive bacteria, *S. aureus* is intrinsically resistant to the TP, owing to its thick peptidoglycan
152 layer preventing membrane-attack complex (MAC) formation and subsequent bacterial lysis.
153 The complement efficacy then only relies on its opsonization effect. However, *S. aureus* can
154 also prevent CP activation by producing the staphylococcal protein A (SpA) (Kronvall and
155 Gewurz 1970) and the second binding protein for immunoglobulins (Sbi) (Zhang *et al.* 1998),
156 which inhibit Ig interaction with C1q, as described for the staphylococcal superantigen-like
157 protein 10 (SSL10) (Itoh *et al.* 2010). Interestingly, SSL10 was also shown to bind
158 prothrombin and factor Xa *in vitro* via their γ -carboxyglutamic acid (Gla) domain, interfering
159 with the activation of the coagulation cascade (Itoh *et al.* 2013) (Supplementary Table 8).
160 Aside from complement subversion, SpA also suppresses B cell response during
161 bloodstream infection (Kim *et al.* 2015). Remarkably, *S. aureus* has been shown to target all
162 C3 and C5 convertases from CP/LP and AP by expressing factors such as the extracellular
163 adherence protein Eap that binds to C4b and prevents the formation of the C3 proconvertase
164 C4b2 (Woehl *et al.* 2014), the staphylococcal complement inhibitor protein SCIN that blocks
165 C4b2b and C3bBb(P) formation and function (Rooijackers *et al.* 2005b; Jongerius *et al.* 2007),
166 the extracellular complement-binding protein Ecb and the extracellular fibrinogen-binding
167 protein Efb which also inhibit the C3 convertase C3bBb(P) as well as C5 convertases
168 C4b2bC3b and C3bBbC3b activity (Jongerius *et al.* 2007), thereby promoting bloodstream
169 infection in a murine infection model (Jongerius *et al.* 2012). *S. aureus* produces another
170 factor preventing opsonization, the staphylokinase, which binds and activates plasminogen
171 into plasmin, leading to C3b and IgG degradation (Rooijackers *et al.* 2005a). Sbi and Efb also
172 bind plasmin, triggering C3a, C3 and C3b degradation and resulting in reduced chemotaxis
173 (Koch *et al.* 2012). By interacting with human fibrinogen, Efb promotes formation of a capsule-
174 like structure which hampers C3b deposition and opsonophagocytosis (see next section) (Ko
175 *et al.* 2013). Additionally, *S. aureus* expresses two small proteins, the superantigen like
176 protein 7 (SSL7) and CHIPS (chemotaxis inhibitory protein of *Staphylococcus*), which bind
177 C5 and C5aR, respectively, thereby interfering with C5a signaling and abrogating C5a-
178 dependent chemotaxis (De Haas *et al.* 2004; Bestebroer *et al.* 2010).

179 Gram-negative bacteria evolved specific strategies to prevent MAC insertion in their outer
180 membrane (OM) and overcome complement activation. *E. coli*, the bacterium the most
181 frequently isolated from blood worldwide, produces the TraT protein, which inhibits C5b-C6
182 interaction, thereby preventing MAC assembly and promoting bacterial survival in serum
183 (Pramoonjago *et al.* 1992). Lipopolysaccharide (LPS), in particular O-antigen, also
184 contributes to complement resistance, possibly through reduction of membrane fluidity
185 affecting MAC insertion (Taylor 1983) or deposition of complement components and MAC
186 away from the OM, as it has been shown in several *S. enterica* serotypes (Joiner *et al.* 1982,
187 1986) and *K. pneumoniae* (Merino *et al.* 1992). This relates to the observation that rough
188 strains of *E. coli* that lack O-antigen are more sensitive to serum than smooth strains, in which
189 LPS contains O-antigen (Johnson 1991). LPS can also interfere with the CP and LP. The
190 LPS structure is believed to determine the level of binding of MBL, which is reduced by O-
191 antigen and sialic acid in *Neisseria gonorrhoeae* and *S. enterica* serovar Typhimurium
192 (Devyatyarova-Johnson *et al.* 2000). *H. influenzae* prevents IgM binding by altering the
193 structure of its lipooligosaccharide (LOS - a particular type of LPS that lacks O-antigen)
194 through incorporation of galactose, thereby reducing complement activation and neutrophil-
195 mediated killing (Langereis and Weiser 2014). Furthermore, the phase-variable LOS
196 biosynthesis gene *igtC* is necessary to minimize C4b deposition on *H. influenzae* surface (Ho
197 *et al.* 2007). Bacterial surface structures, such as capsule, exopolysaccharide (EPS) or LPS
198 can prevent C3/C3b deposition and opsonization, thereby reducing phagocytosis and
199 promoting survival in blood. The bacterial components involved in these mechanisms are
200 detailed in the section 'Phagocytosis escape'.

201 Degradation of complement components is another mechanism evolved by major
202 bacteria responsible for bloodstream infection. For instance, *Streptococcus pyogenes*
203 peptidase ScpA can cleave C3, C3a and C5a (Lynskey *et al.* 2017) and *E. coli* Pic
204 autotransporter cleaves C2, C3, C3b, C4 and C4b (Abreu *et al.* 2015). However, a recent
205 study underlined the importance of *in vivo* validation of effector activity demonstrated *in vitro*.
206 Indeed, while *P. aeruginosa* alkaline protease AprA (or PaAP) degrades C1q, C3 (Hong and

207 Ghebrehiwet 1992), C1s and C2 (Laarman *et al.* 2012), and the elastase LasB (or PaE)
208 degrades C1q and C3 (Hong and Ghebrehiwet 1992) *in vitro*; AprA- and LasB-deficient
209 mutants are as virulent as a their parental strain in several animal models (Mateu-Borrás *et*
210 *al.* 2022).

211 Interestingly, a recent study reported that Gram-negative bacteria such as *P. aeruginosa*,
212 *A. baumannii*, *B. multivorans*, enteroaggregative *E. coli*, *K. pneumoniae* and *Y. enterocolitica*,
213 can form sub-populations of complement evaders, which present a biphasic survival curve
214 when exposed to serum and increased resistance to MAC (Pont *et al.* 2020). Mutants in genes
215 of purine and biotin biosynthesis were further identified as persistence enhancers, while
216 mutants in polyphosphate kinase genes had a decreased number of evaders upon incubation
217 in plasma, establishing a link between metabolism and complement evasion (Janet-Maitre *et*
218 *al.* 2023).

219

220 **Recruitment of complement inhibitors**

221 A common strategy used by bacteria to evade complement is the recruitment of
222 complement inhibitors that regulate autologous complement activation to prevent
223 inflammation and pathologies. For example, *E. coli* secretes the metalloprotease StcE that
224 recruits and potentiates C1-INH, a serine protease inhibitor that negatively regulates C1r, C1s
225 (CP), MASP-1 and MASP-2 (LP) on host cells, protecting adherent bacteria from complement
226 (Lathem *et al.* 2004).

227 A majority of bacteria involved in bloodstream infections produces factors that interact
228 with C4BP, the main negative regulator of CP and LP, to prevent complement activation, such
229 as *E. coli* OmpA and Nlpl (Wooster *et al.* 2006; Tseng *et al.* 2012). C4BP binding to *N.*
230 *gonorrhoeae* porins Por1A and PorB1 and *Neisseria meningitidis* PorA has also been
231 demonstrated to confer serum resistance (Ram *et al.* 2001; Jarva *et al.* 2005). In addition,
232 gonococcal LOS structure plays a role in C4BP binding efficiency, as shown by a heptose
233 glycan substitution enhancing serum resistance (Ram *et al.* 2007) or phosphoethanolamine
234 residues from the lipid A promoting C4BP binding to PorB (Lewis *et al.* 2013).

235 The main negative regulators of the AP, i.e., factor H (fH), factor H-like (FHL-1) and factor
236 H-related protein (FHR-1) (Ferreira et al. 2010), are also subverted by bacterial determinants
237 of bloodstream infection, such as *A. baumannii* OmpA (Kim et al. 2009b), *E. coli* OmpW (Li
238 et al. 2016) or *N. meningitidis* factor H binding protein fHBP (Madico et al. 2006). *N.*
239 *meningitidis* NspA protein whose expression was initially shown to be induced in human blood
240 (Echenique-Rivera et al. 2011), was later demonstrated to interact with factor H, like sialylated
241 LOS, promoting serum resistance in *N. meningitidis* and *N. gonorrhoeae* (Lewis et al. 2012;
242 Giuntini et al. 2015; Lewis et al. 2019). *S. aureus* has been shown to subvert both C4BP- and
243 fH-mediated inhibition of complement. Indeed, staphylococcal clumping factor ClfA recruits
244 factor I, the protease responsible for degradation of C4b via C4BP (CP and LP) and
245 degradation of C3b via factor H (AP) (Hair et al. 2008), decreasing complement activation
246 and opsonization. Interestingly, ClfA also allows staphylococci to associate with the fibrin
247 cables resulting from the activation of prothrombin by the coagulases Coa and von Willebrand
248 factor binding protein vWbp, ultimately promoting agglutination and infection severity in a
249 mouse model of sepsis (McAdow et al. 2011) (Supplementary Table 8).

250 Inhibitors of MAC assembly such as heparin-regulated vitronectin, clusterin, COMP or
251 CD59, can also be recruited or mimicked by bacteria. For instance, the Ldp moonlighting
252 protein of *P. aeruginosa* binds both clusterin and vitronectin to inhibit the TP and promote
253 bacteria survival in serum (Hallström et al. 2015).

254 Strikingly, some bacterial factors can inhibit CP, LP and AP by simultaneously binding to
255 C4BP and fH such as *S. aureus* SrdE/Bbp (Sharp et al. 2012). Pathogenic *Yersinia* species
256 and several *S. enterica* serotypes encode Ail and Rck proteins, respectively, which are
257 homologous proteases shown to bind fH, C4BP, heparin, and to recruit vitronectin, inhibiting
258 MAC formation by blocking its insertion and C9 polymerization. This mechanism enhances
259 serum resistance in *S. enterica* (Heffernan et al. 1992; Ho et al. 2010; Ho et al. 2011), *Y.*
260 *pestis* (Bartra et al. 2008, 2015; Ho et al. 2014; Shin et al. 2019; Thomson et al, 2019),
261 *Yersinia enterocolitica* (Bliska and Falkow 1992; Biedzka-Sarek et al. 2008; Kirjavainen et al.
262 2008) and *Yersinia pseudotuberculosis* (Ho et al. 2012). However, these interactions have

263 recently been shown to play a minor role in *Y. pestis* resistance to complement, while
264 maintenance of membrane integrity by Ail contributes to serum resistance (Kolodziejek et al.
265 2022).

266

267 **Combined subversion of complement activation and inhibition**

268 Some bacterial factors are Swiss army knives able to interact with multiple components
269 and regulators of the different complement pathways, allowing protection at different levels of
270 the activation cascades. For example, the *S. enterica* protease PgtE cleaves C3b, C4b, C5
271 (Ramu *et al.* 2007), C3, factor B and factor H (Riva, Korhonen and Meri 2015), promoting
272 serum survival. Intriguingly, PgtE is a homolog of *Yersinia pestis* virulence factor Pla that has
273 been shown to activate plasminogen but does not affect bacterial survival in serum nor during
274 bloodstream infection (Sebbane *et al.* 2006; Sebbane, Uversky and Anisimov 2020). *S.*
275 *pyogenes* protease SpeB cleaves C1-INH, C2, C3, C3b, C4, C5a, C6, C7, C8, C9 and
276 degrades properdin, assuring inactivation of complement at all stages of the cascade (Tsao
277 *et al.* 2006; Kuo *et al.* 2008; Terao *et al.* 2008).

278 Other mechanisms such as complement exhaustion by outer membrane vesicles (OMV)
279 have been described in bacteria (Supplementary Table 5), but their significance during
280 bloodstream infection remains to be determined. Additionally, new bacterial determinants of
281 complement resistance, including envelop components, are currently under investigation
282 (Supplementary Table 6).

283

284 **Bacterial factors subverting blood cell defenses**

285 In addition to the complement system, bacteria are confronted with innate immune cells
286 when entering the bloodstream. Many of these cells are patrolling neutrophils and monocytes
287 involved in phagocytic killing of microbes, and platelets which carry out haemostasis and
288 antimicrobial functions (Jenne *et al.* 2013; Yeaman 2014). Bacteria engaged in bloodstream
289 infection display factors allowing phagocyte or platelet subversion. In this section, we highlight
290 the main subversion mechanisms discovered to date and illustrated in Figure 6. Extensive
291 inventories of factors subverting phagocytes and platelets can be found in Supplementary
292 Tables 7 and 8, respectively.

294 **Phagocytosis escape**

295 Complement and antibodies play an important role in phagocytosis through opsonization
296 of bacteria via C3b or IgG for example, facilitating their uptake by monocytes/macrophages
297 and neutrophils. This phenomenon called opsonophagocytosis is widely counteracted by
298 bacterial factors inhibiting complement action described in the previous section and by the
299 capsule expressed by some bacteria. The effect of *S. enterica* capsule on
300 opsonophagocytosis was described almost 90 years ago (Bhatnagar 1935; Felix and
301 Bhatnagar 1935). Capsule production decreases opsonin deposition, lowering uptake by
302 neutrophils upon interaction with *Bacillus anthracis* (Sharma *et al.* 2020), *E. coli* (Horwitz and
303 Silverstein 1980; Sarkar *et al.* 2014), *K. pneumoniae* (Álvarez *et al.* 2000), *B. pseudomallei*
304 (Reckseidler-Zenteno *et al.* 2005), and some *Streptococcus* species (Locke *et al.* 2007;
305 Hyams *et al.* 2010), as well as uptake by macrophages or monocytes in contact with *E. coli*
306 (Horwitz and Silverstein 1980; Sarkar *et al.* 2014), *H. influenzae* (Noel *et al.* 1996), *S. enterica*
307 (Wilson *et al.* 2011; Hart *et al.* 2016) and *S. aureus* (Thakker *et al.* 1998). Interestingly, a
308 recent report highlighted cell-type dependent effects of *S. enterica* Vi capsule, which was
309 shown to inhibit phagocytosis by human neutrophils and to promote human macrophage
310 phagocytosis by binding DC-SIGN lectin (Zhang *et al.* 2022). It has also been suggested that

311 the capsule can mask C3 deposited on the cell wall from phagocyte receptors (Watts *et al.*
312 2005; Thurlow *et al.* 2009), as well as hide pathogen-associated molecular patterns (PAMPs)
313 such as lipoteichoic acid (LTA) or peptidoglycan (PG) from pattern recognition receptors
314 (PRRs), dampening immune responses (Thurlow *et al.* 2009). Furthermore, a recent report
315 showed that inactivation of the glycosyltransferase Gtr6 of a hypervirulent *A. baumannii*
316 clinical isolate modifies capsule acetylation and protects bacteria from C3b deposition,
317 phagocytosis in vitro and clearance from blood in vivo, resulting in lethal infection in mice
318 (Talyansky *et al.* 2021). This study highlights the importance and possible evolution of
319 bacterial surface structure for immune escape. Other surface factors reducing
320 opsonophagocytosis include enterococcal polysaccharide (EPA) (Xu *et al.* 2000; Smith *et al.*
321 2019), and exopolysaccharide (EPS) (Mishra *et al.* 2012) or proteins such as *S. pneumoniae*
322 neuraminidase NanA acting on human glycoconjugates at the surface of bacteria to reduce
323 C3 deposition (Dalia *et al.* 2010).

324 Apart from the opsonization decrease, pathogens evolved other mechanisms to prevent
325 phagocytosis such as binding to fibronectin and/or to fibrinogen (Palmqvist *et al.* 2004;
326 Higgins *et al.* 2006; Jung *et al.* 2009), or to erythrocyte CR1, protecting bacteria from uptake
327 (Brekke *et al.* 2011). For example, the enterococcal surface protein ElrA reduces bacterial
328 adherence to macrophages and internalization (Cortes-Perez *et al.* 2015). In contrast,
329 *Streptococcus suis* protein HP0487 was recently shown to promote neutrophil adhesion while
330 reducing phagocytosis (Hui *et al.* 2021). Interestingly, *S. aureus* and *B. anthracis* lacking the
331 adenosine synthase A AdsA have a reduced capacity to prevent phagocytic clearance in
332 blood. Abscess formation by *S. aureus* was dependent on AdsA and could be rescued in an
333 *adsA* mutant by exogenous supply of adenosine, a known immune regulator. This suggests
334 that these pathogens can subvert phagocytic clearance by controlling adenosine levels
335 (Thammavongsa *et al.* 2009).

336

337

338 **Phagocyte and platelet impairment**

339 Bacteria involved in bloodstream infection can directly target phagocytes and platelets to
340 prevent phagocytosis and immune response. For example, *S. aureus* can lyse neutrophils by
341 producing small cytotoxic alpha-helical peptides called phenol-soluble modulins (PSMs)
342 (Wang *et al.* 2007). It has been further shown that the leucocidin LukED directly kills
343 phagocytes, thereby promoting bloodstream infection in mice (Alonzo *et al.* 2012). Expression
344 of gamma hemolysin HlgABC is highly upregulated in human blood and contributes to lysis
345 of human neutrophils upon secretion by extracellular *S. aureus*. However, HlgABC has a
346 modest contribution to virulence in a mouse bacteremia model of infection, presumably due
347 to functional redundancy with other leukotoxins (Malachowa and DeLeo 2011; Malachowa *et*
348 *al.* 2011). An indirect phagocyte targeting mechanism was recently discovered, involving the
349 staphylococcal superantigens (Sags) which promote bloodstream infection through
350 modulation of IFN- γ production by CD4-positive T cells, impairing macrophage function in the
351 liver and bacterial clearance (Tuffs *et al.* 2022).

352 Some Gram-negative bacteria involved in bloodstream infection directly inject cytotoxic
353 effectors into the cytoplasm of phagocytes. For example, *Y. pestis* intoxicates macrophages
354 and neutrophils via injection of the *Yersinia* outer proteins (Yops) by its type 3 secretion
355 system (T3SS) during bloodstream infection (Marketon *et al.* 2005). These Yops display
356 antiphagocytic properties and can trigger apoptosis and pyroptosis of immune cells,
357 promoting infection (Pinaud *et al.* 2018; Demeure *et al.* 2019; Chen and Brodsky 2023).
358 Among Yops, YopM has been shown to inhibit thrombin and ristocetin-induced platelet
359 aggregation (Leung *et al.* 1990; Palace *et al.* 2020). This latter study also highlighted the role
360 of the plasminogen activator Pla in this mechanism. However, Pla has previously been shown
361 to be dispensable in a septicemic plague model (Sebbane *et al.* 2006). Similar to *Y. pestis*,
362 *P. aeruginosa* T3SS-injected Tox effectors are required for survival in blood (Vance *et al.*
363 2005). *S. enterica* SPI-2 T3SS and non-typhoid strain Spv effectors enable systemic infection
364 by promoting the intracellular lifestyle of bacteria and impairing phagocyte survival (Guiney

365 and Fierer 2011; Jennings et al. 2017; Pinaud et al. 2018). Yet, their exact roles in
366 bloodstream dissemination and survival in blood remain to be clarified.

367 While the immune role of platelets has long been overlooked, a recent study described a
368 new factor playing a dual role in platelet resistance by *Streptococcus agalactiae*. Indeed, sialic
369 acids (Sia) decorating its capsule polysaccharide (CPS) promote resistance to platelet killing
370 and particularly to platelet antimicrobial peptides. Moreover, Sia bind platelet lectin Siglec-9,
371 thereby inhibiting their activation and promoting *S. agalactiae* blood infection (Uchiyama et
372 al. 2019).

373 Aggregation and exhaustion of neutrophils can be triggered to evade phagocytes, as
374 reported with *S. suis* muramidase-released protein MRP, which interacts with human
375 fibrinogen, and subsequently with neutrophils via an $\alpha_x\beta_2$ integrin-dependent mechanism
376 (Pian et al. 2016). Similar strategies are used to deplete platelets from the bloodstream
377 leading to thrombocytopenia. Dysregulation of platelet activation is a mechanism shared by
378 various bacteria such as *B. anthracis*, whose peptidoglycan activates platelets in a Fc γ RII-
379 and complement-dependent manner (Sun et al. 2013), contributing to the disseminated
380 intravascular coagulation (DIC) necessary for *B. anthracis* pathogenesis (Qiu et al. 2013). *In*
381 *vitro* studies of staphylococcal SSL5 also showed activation of platelets through glycoproteins
382 Iba and α IIb β 3 interaction (De Haas et al. 2009). The pneumococcal neuraminidase NanA,
383 mentioned in the previous section, also removes surface sialic acids from cells, increasing
384 platelets activation as well (Syed et al. 2019).

385 Interestingly, *S. pyogenes* was recently shown to induce thrombocytopenia by a new
386 mechanism exploiting phagocytes. The streptococcal M1 protein is indeed able to form a
387 complex with fibrinogen, Ig and complement components in plasma, and to bind to platelet
388 surface, thus enhancing their phagocytosis by monocytes (Palm et al. 2019).

389

390

391 **Resistance to phagocyte defenses**

392 Many bacteria that do not escape phagocytosis or cannot impede immune cells produce
393 factors preventing intracellular killing. Reactive oxygen species (ROS) are among the most
394 potent weapons of phagocytic cells. Bacteria evolved mechanisms to counteract ROS-
395 mediated toxicity. For instance, *S. aureus* synthesizes the antioxidant staphyloxanthin (STX),
396 a membrane-embedded carotenoid pigment which enhances resistance to ROS produced by
397 phagosomal NADPH oxidase NOX2, promoting bacterial survival in phagocytes and virulence
398 (Hall *et al.* 2017). The antioxidant activity of superoxide dismutases (SOD) SodA, SodB
399 and/or SodC also plays a role in ROS resistance and virulence in *S. enterica* (De Groot *et al.*
400 *et al.* 1997; Farrant *et al.* 1997; Fang *et al.* 1999; Ammendola *et al.* 2005), *V. vulnificus* (Kang
401 *et al.* 2007), *B. pseudomallei* (Vanaporn *et al.* 2011), *S. agalactiae* (Poyart *et al.* 2001; Zhu *et al.*
402 *et al.* 2020), *S. suis* (Tang *et al.* 2012), *N. meningitidis* (Wilks *et al.* 1998), and *Y. enterocolitica*
403 (Roggenkamp *et al.* 1997). While *S. aureus* superoxide dismutase activity was not correlated
404 with virulence *in vivo*, its catalase activity protected bacteria against neutrophil killing (Mandell
405 1975). Specific catalases were thereafter shown to promote infection such as leptospiral KatE
406 (Eshghi *et al.* 2012), *P. aeruginosa* KatA (Kim *et al.* 2009a) or *H. influenzae* HktE (Bishai *et al.*
407 *et al.* 1994). Singularly, *S. aureus* can exist as small-colony variants (SCVs), which often lack a
408 functional electron transport chain and do not produce leucocidins, hemolysins and STX.
409 Despite absence of these virulence factors, SCVs can survive in blood due to their reduced
410 sensitivity to neutrophil oxidative burst linked to their defective electron transport system. This
411 observation was confirmed by electron transport restoration in a strain of *E. faecalis* whose
412 electron transport chain was naturally non-functional, leading to a decreased survival in blood
413 (Painter *et al.* 2017).

414 Glutamate also plays an important role in ROS resistance. When converted to
415 glutathione, it allows a balanced intracellular redox potential promoting *N. meningitidis*
416 bacteremia and resistance to neutrophil ROS (Talà *et al.* 2011). This mechanism emphasizes
417 the importance of glutamate importers such as GltT or NMB1966 in *N. meningitidis* virulence

418 potential (Sun *et al.* 2000; Li *et al.* 2009; Talà *et al.* 2011; Capel *et al.* 2017). Along the same
419 line, the glutamate dehydrogenase GdhA, which is upregulated when *N. meningitidis* is grown
420 in whole blood (Echenique-Rivera *et al.* 2011), was shown to be required for systemic
421 infection (Sun *et al.* 2000; Liu *et al.* 2016; Capel *et al.* 2017). Interestingly, *S. enterica* ortholog
422 of GdhA has recently been shown to convert ammonia to glutamate which is in turn converted
423 to glutathione, promoting resistance to ROS and intracellular survival (Huang *et al.* 2022),
424 which could explain the contribution of GdhA in *N. meningitidis* pathogenicity.

425 In addition to ROS, phagolysosome acidic environment plays a role in pathogen killing.
426 *S. enterica* withstands phagosomal acidity by producing the virulence protein MgtC. In
427 contrast to other effectors, MgtC does not target vacuolar ATPase but it binds bacterial F₁F_o
428 ATP synthase, inhibiting proton translocation and ATP synthesis allowing maintenance of a
429 physiological ATP level and intracellular pH by bacteria replicating inside acidic phagosomes
430 and thereby promoting systemic infection (Lee *et al.* 2013). The role of this mechanism in
431 bacteremia remains to be fully deciphered. Neutrophils can also trigger NETosis, a specific
432 cell death program that promotes formation of neutrophil extracellular traps (NET) by
433 releasing a net made of DNA, histones, granular proteins and antimicrobial peptides, trapping
434 and degrading microbes (Vorobjeva and Chernyak 2020). Some bacteria encode
435 endonucleases or DNases to evade NETs, increasing their survival in blood, such as for *S.*
436 *pyogenes* Sda1 DNase (Buchanan *et al.* 2006).

437 Antimicrobial metal sequestration or intoxication by phagocytes and their subversion by
438 bacteria will be developed in the section 'Bacterial factors subverting nutritional immunity'.
439

440 **Antimicrobial peptide resistance factors**

441 Antimicrobial peptides (AMPs) are defense components of all living organisms that can
442 kill not only bacteria, but also viruses, parasites and fungi by a variety of mechanisms
443 including membrane destabilization (Bahar and Ren 2013). Resistance to AMPs contributes
444 to the subversion of the immune system by bacteria during the blood phase of infection.
445 Bacterial factors promoting resistance to AMPs and survival in blood or systemic infection are
446 presented in Supplementary Table 9.

447

448 **Factors modifying the charge of bacterial surface**

449 An AMP resistance mechanism widely used by bacteria consists in reduction of the
450 negative charge of their surface, preventing the electrostatic attraction of cationic defense
451 molecules. This is in part mediated by expression the *dltABCD* operon and the *mprF* gene,
452 responsible for D-alanylation of teichoic acids and lysinylation of membrane
453 phosphatidylglycerol, respectively, in Gram-positive bacteria such as *S. agalactiae* (Poyart *et*
454 *al.* 2003), *S. pneumoniae* (Kovács *et al.* 2006; Wartha *et al.* 2007), *S. suis* (Fittipaldi *et al.*
455 2008), *B. anthracis* (Fisher *et al.* 2006; Samant *et al.* 2009), *S. aureus* (Collins *et al.* 2002;
456 Weidenmaier *et al.* 2005) and *L. monocytogenes* (Abachin *et al.* 2002; Thedieck *et al.* 2006).
457 In *S. aureus*, this surface charge modification is associated with increased resistance to
458 endogenous cationic antimicrobial peptides, such as α -defensins, and to thrombin-induced
459 platelet microbicidal protein 1 (tPMP-1), promoting infection in a rabbit endocarditis model
460 (Weidenmaier *et al.* 2005).

461 Interestingly, a similar mechanism of amino acid addition to the lipid A, enhancing AMP
462 resistance and intestinal colonization, has been more recently described in *V. cholerae*
463 (Hankins *et al.* 2012; Herrera *et al.* 2014). However, its implication in bloodstream infection
464 remains to be elucidated. Reduction of the negative charge of LPS or LOS lipid A, via
465 aminoarabinose addition for example, is a common mechanism of AMP resistance among
466 Gram-negative bacteria (Needham and Trent 2013). While this mechanism can play a role in

467 virulence via peripheral route of infection (Gunn *et al.* 2000), few studies have highlighted its
468 importance in blood survival. For example, the loss of phosphoethanolamine (PEA)
469 substitution from *N. gonorrhoeae* lipid A mediated by the PEA transferase LptA, has been
470 shown to increase susceptibility to polymyxin B, but the observed increased sensitivity to
471 serum killing was mainly due to the classical complement pathway (Lewis *et al.* 2009).

472 *N. meningitidis* fHBP is also involved in resistance to the antimicrobial peptide LL-37,
473 which could be mediated by their electrostatic interactions (Seib *et al.* 2009), besides its
474 aforementioned key role in complement inhibition.

475

476 **Potassium transporters**

477 Interestingly, the potassium importer Trk/Sap is an AMP resistance factor shared by
478 several bacterial species, possibly by maintaining potassium homeostasis while AMPs target
479 the bacterial surface. The *V. vulnificus trkA* potassium transport gene has been shown to be
480 involved in resistance to AMPs such as protamine or polymyxin B, and to contribute to serum
481 resistance and virulence in mouse models of infection (Chen *et al.* 2004). The SapG
482 potassium transporter of *S. enterica* serovar Typhimurium also contributes to protamine
483 resistance (Parra-Lopez *et al.* 1994) and virulence in a mouse model of infection (Groisman
484 *et al.* 1992). While the exact mechanism of resistance remains unknown, it was suggested
485 that *S. enterica* secreted virulence factors were regulated by the Trk transporter (Su *et al.*
486 2009). Additionally, a genome-wide screen highlighted the importance of the *sapABCDF*
487 operon for *E. coli* systemic infection in mice (Subashchandrabose *et al.* 2013). AMP
488 resistance *in vitro* or *in vivo* mediated by a similar transporter has been reported in *Y.*
489 *enterocolitica* (Bengoechea and Skurnik 2000) and *H. influenzae* (Mason, Munson and
490 Bakaletz 2005; Mason *et al.* 2006). However, its role in bloodstream infection was not
491 assessed.

492

493

494 **Other mechanisms of resistance to AMPs**

495 AMPs can act in several bodily fluids as well as intracellularly, in particular in phagosome
496 in which they contribute to kill bacteria. PilB, the major pilus protein of *S. agalactiae* has been
497 shown to mediate resistance to LL-37, presumably upon sequestering the AMP, promoting
498 resistance to neutrophil killing, survival in macrophages and bloodstream infection (Maisey *et*
499 *al.* 2008).

500 Several studies have identified new AMP resistance factors whose mechanisms of action
501 remain to be deciphered. They are listed in Supplementary Table 9.

502

503 **Bacterial factors subverting nutritional immunity**

504 Metals are essential structural and catalytic cofactors of proteins involved in cellular
505 homeostasis in all living organisms. Pathogenic bacteria evolved mechanisms to subvert
506 nutritional immunity by which host controls infection through metal limitation and intoxication
507 (Murdoch and Skaar 2022) (Figure 7, Supplementary Table 10).

508

509 **Iron**

510 Iron (Fe) has been identified as one of the key metals regulating virulence in pathogenic
511 bacteria reaching the bloodstream, where iron is mainly bound to transferrin and to heme in
512 hemoproteins such as hemoglobin. Bacteria have developed diverse highly efficient systems
513 to capture iron from host iron-binding proteins (Murdoch and Skaar 2022). Secretion and
514 uptake of siderophores, which are high affinity metal ion chelators, is an efficient mechanism
515 of iron acquisition that is widespread in bacteria. The *Serratia marcescens* siderophore
516 serratiochelin is required for growth in human serum and bacteremia (Weakland *et al.* 2020).
517 The ferric enterobactin receptor FepA was identified as essential for *A. baumannii* virulence
518 along with the iron transporter FeoB using a TRaDIS screen in a mouse model of bacteremia
519 (Subashchandrabose *et al.* 2016). The operon of the previously mentioned siderophore Ybt

520 is located on a mobile element, the high pathogenicity island (HPI) that was horizontally
521 acquired by or from other bacteria such as APEC or ExPEC, in which Ybt has recently been
522 shown to promote bloodstream infection (Huja *et al.* 2015; Johnson *et al.* 2018). In *K.*
523 *pneumoniae* Ybt is not essential for serum survival in contrast to enterobactin and
524 salmochelin (Bachman *et al.* 2011). In Gram-negative bacteria, import of siderophores and
525 other molecules widely relies on the TonB-ExbB-ExbD system allowing energy transduction
526 through the envelope. *A. baumannii* TonB3 was indeed shown to contribute to bacterial serum
527 survival and virulence (Runci *et al.* 2019). A similar role was uncovered in *K. pneumoniae*
528 (Hsieh *et al.* 2008), *N. meningitidis* (Sun *et al.* 2000; Capel *et al.* 2017) and *Y. pestis* (Palace
529 *et al.* 2014).

530 To acquire iron, some bacteria also possess ferrous and ferric iron transporters. Some of
531 them are required for full virulence and blood survival, such as the SitABCD ATP-binding
532 cassette (ABC) transporter mediating uptake of ferrous iron and manganese through the inner
533 membrane (IM) in avian pathogenic *E. coli* (Sabri *et al.* 2008) and *S. enterica* (Boyer *et al.*
534 2002; Zaharik *et al.* 2004). In contrast, mutation of *Y. pestis* *yfe* iron IM transporter gene does
535 not reduce virulence in a model of septicemic plague. However, inactivation of both *Yfe* and
536 *yersiniabactin* leads to virulence attenuation in this model, suggesting a redundancy of these
537 iron import systems since Ybt is not required for septicemic plague (Perry *et al.* 2015).

538 Other bacteria produce factors that directly capture transferrin or heme to circumvent free
539 iron scarcity in the blood. For example, the *N. meningitidis* transferrin binding protein TbpA is
540 essential for virulence in a mouse model of bacteremia, and for bacterial growth in human
541 blood (Renauld-Mongénie *et al.* 2004; Bidmos *et al.* 2015).

542 *N. meningitidis* iron uptake also relies on the hemoglobin receptor HpuAB and HmbR, a
543 second hemoglobin binding protein, required for virulence in a rat model in absence of HpuAB
544 (Stojjkovic *et al.* 1995). However, this phenotype was not reproduced when assessing early
545 bacterial survival in human blood, contrary to TbpA, suggesting a role of HmbR in later stages
546 of the infection process when blood transferrin levels decrease and hemoglobin levels
547 increase due to erythrocyte lysis (Bidmos *et al.* 2015). The streptococcal hemoprotein

548 receptor protein Shr has also been demonstrated to be important for iron uptake in human
549 blood and for *S. pyogenes* virulence in mouse models of skin and systemic infection (Dahesh
550 et al. 2012). Likewise, the surface hemoglobin receptor IsdB transfers iron bound heme to
551 other Isd components and eventually inside *S. aureus*. IsdB is required for full virulence in
552 various mouse models (Torres *et al.* 2006; Pishchany *et al.* 2010, 2014). In *S. aureus*
553 leucocidins LukED and HlgAB bicomponent toxins have been involved in iron acquisition as
554 they lyse erythrocytes by targeting the Duffy antigen receptor for chemokines (DARC).
555 Consequently, these toxins promote growth of *S. aureus* in a hemoglobin-acquisition-
556 dependent manner and contribute to infection in mice (Spaan *et al.* 2015).

557

558 **Manganese**

559 Manganese (Mn) is another metal cofactor required for all forms of life. It can be
560 sequestered by immune cell effectors such as calprotectin, thereby reducing Mn-cofactored
561 superoxide dismutase activity and oxidative stress resistance, as shown in *Streptococcus*
562 *sanguinis* (Crump *et al.* 2014; Zhu *et al.* 2021). Bacteria produce several broadly conserved
563 classes of Mn importers. The Natural Resistance-Associated Macrophage Protein (NRAMP)
564 family is a major class of proton-powered Mn importers expressed in mammals, plants,
565 insects and bacteria in which they are generally named MntH. Both MntH and SitABC
566 transport systems have been shown to play an important role in *S. enterica* virulence in
567 NRAMP1 expressing mice, while MntH was not required in a SitABC mutant background and
568 in NRAMP1 defective mice which cannot deplete Mn and Fe from intracellular compartments
569 (Boyer *et al.* 2002; Zaharik *et al.* 2004). In a similar competition scenario, *S. aureus* MntH and
570 MntABC transporters have been shown to be induced in presence of calprotectin during the
571 course of systemic infection (Kehl-Fie *et al.* 2013).

572 High amounts of Mn can also be toxic for bacteria, as highlighted by the importance of
573 the *N. meningitidis* Mn²⁺ exporter MntX in regulating the intracellular Mn/Fe ratio and
574 preventing manganese toxicity, which is exacerbated in low iron conditions. MntX was shown
575 to be important to resist killing by human serum and for bacterial survival in mouse blood in

576 a model of septicemia following intraperitoneal inoculation (Veyrier *et al.* 2011). More recently,
577 MntE, a member of the cation diffusion facilitator protein family, was shown to prevent
578 excessive intracellular Mn accumulation. Deletion of the MntE gene led to a reduced tolerance
579 to oxidative stress and decreased virulence during systemic infection with *S. suis* (Xu *et al.*
580 2017) and *S. aureus* (Grunenwald *et al.* 2019). The latter study linked Fe homeostasis to Mn
581 efflux.

582

583 **Zinc**

584 Similar to Fe and Mn, zinc (Zn) is an important cofactor for various enzymes, such as
585 superoxide dismutases, and is also sequestered by the host immunity protein calprotectin.
586 Bacteria subvert this restriction by expressing Zn importers. For example, the AdcABC
587 transporter is required for Zn import into the cytoplasm of Gram-positive bacteria and
588 promotes blood survival and systemic infection in several *Streptococcus* species (Bayle *et al.*
589 2011; Le Breton *et al.* 2013; Ong *et al.* 2018; Zhu *et al.* 2020). The high affinity IM zinc
590 transporter ZnuABC is required for systemic infection with the Gram-negative *S. enterica*
591 (Ammendola *et al.* 2007) in synergy with the low affinity Zn transporter ZupT (Cerasi *et al.*
592 2014). While outer membrane (OM) crossing has long been overlooked, it has been observed
593 that the conserved outer membrane protein (OMP) zinc-uptake component D ZnuD is induced
594 when *N. meningitidis* is incubated in whole blood (Echenique-Rivera *et al.* 2011). ZnuD
595 functions as a gated pore in the OM, importing Zn ions (Calmettes *et al.* 2015). ZnuD is
596 required for efficient systemic infection with *N. meningitidis* (Calmettes *et al.* 2015) and *A.*
597 *baumannii* (Hesse *et al.* 2019). However, the latter study highlighted different contributions of
598 OMP ZnuD and IM ZnuABC depending on infected tissues.

599 Similar to *yfe*, a deletion of *znuABC* alone is not sufficient to reduce *Y. pestis* virulence in
600 a model of septicemic plague. However, the HMWP2 protein involved in Ybt siderophore
601 production is required for growth of a *znuABC* mutant in zinc-deficient conditions and for
602 septicemic plague. It has been suggested that the Zn-binding siderophore Ybt may serve as
603 a zincophore for Zn²⁺ acquisition which also relies on YbtX, a member of the major facilitator

604 superfamily (Bobrov *et al.* 2014). Similarly, *S. aureus* uses two importers, the AdcABC
605 permease and the CntABCD transporter that can import the metallophore staphylopin (StP),
606 enabling bacteria to compete with the host for zinc and promote systemic infection (Grim *et*
607 *al.* 2017).

608 Zn intoxication can take place as an immune response to infection, and Zn export
609 systems have been evolved by bacteria to survive this toxicity, as exemplified by
610 streptococcal CzcD export protein (Ong *et al.* 2018; Zhu *et al.* 2021). Interestingly, Zn
611 tolerance can differ between bacterial species. Indeed, *S. pyogenes* faces zinc toxicity upon
612 phagocytosis by neutrophils and nutritional immunity extracellularly (Ong *et al.* 2018). In
613 contrast, a *S. sanguinis czcD* mutant showed impaired growth extracellularly in human serum,
614 which contains higher Zn concentration than saliva, the usual commensal niche of *S.*
615 *sanguinis* (Zhu *et al.* 2021).

616

617 **Other metals**

618 Copper is used by macrophages to kill phagocytosed bacteria but is also required as a
619 cofactor of important bacterial enzymes such as Cu/Zn SOD SodC. Many bacteria encode
620 the IM copper exporter CopA (formerly known as CueA), which is required for full virulence in
621 *S. pneumoniae* (Johnson *et al.* 2015) and *P. aeruginosa* (Schwan *et al.* 2005) but not in *S.*
622 *enterica* (Fenlon and Slauch 2017). Several copper resistance factor such as copper exporter
623 or oxidase have been described in *S. enterica* but their involvement in virulence seems strain
624 specific and varies according to the route of infection (Hyre *et al.* 2021). In *L. monocytogenes*
625 the copper transporter CtpA is required to establish a systemic infection, but the exact
626 virulence mechanism remains unknown (Francis and Thomas 1997).

627 Calcium can also be toxic to bacteria that developed mechanisms to regulate its
628 concentration. A *S. pneumoniae caxP* mutant accumulated intracellular calcium and had a
629 defective growth in sheep blood, human plasma and human serum, as well as a reduced
630 virulence in mice (Rosch *et al.* 2008).

631 High level of sodium can be toxic as well, and it has been reported that inactivation of Y.

632 *pestis* Na⁺/H⁺ antiporters NhaA and NhaB abolishes virulence, possibly by sensitizing
633 bacteria to Na⁺ toxicity in blood (Minato *et al.* 2013).

634 Magnesium (Mg) divalent cation has several biological functions, including as an
635 enzymatic cofactor and a neutralizer of negatively charged macromolecules. The magnesium
636 transporter MgtB has been shown to contribute to systemic infection in several *Yersinia*
637 species, as *mgtB* mutants have a low competitive index after intravenous injection (Stubben
638 *et al.* 2009; Ford *et al.* 2014). A similar function of MgtB was more recently described in *S.*
639 *marcescens* (Anderson *et al.* 2017) and *S. enterica* (Choi *et al.* 2017). A recent breakthrough
640 study identified SLC11A1 (NRAMP1) as the main Mg restrictor inside phagocytes leading to
641 resistance against *S. enterica* infection (Cunrath and Bumann 2019). Expectedly, MgtB is
642 required for *S. enterica* virulence in NRAMP1 positive but not in NRAMP1 negative mice.

643 Nickel plays a role in nutritional immunity, being sequestered by calprotectin. As a
644 cofactor of several redox and non-redox enzymes produced by bacteria, it is required for
645 diverse metabolic processes during infection (see next section). A recent transcriptomic study
646 of porcine ExPEC in bloodstream of infected animals and in swine blood *ex vivo* revealed an
647 upregulation of the expression of the nickel transporter NikABCDER, which was also shown
648 to contribute to bacterial growth in swine blood and in infected mice (Ma *et al.* 2020).

649 Cobalt also serves as a cofactor for several bacterial proteins, but its implication in
650 nutritional immunity is unclear. A screen of *S. sanguinis* mutants in human serum identified
651 transporter genes of the energy coupling factor (ECF) family, *ecfA2*, *ecfT*, and *stpA*, whose
652 single mutants and the triple mutant were shown to have decreased survival in human serum
653 (Zhu *et al.* 2021). These genes were annotated as cobalt transporters, but their exact function
654 and substrate remain to be characterized.

655 **Bacterial metabolic factors**

656 Nutrients and compounds vary greatly within hosts, defining multiple biogeochemical
657 microhabitats in which bacteria adapt their metabolism, in particular when they reach the
658 blood during the infection process (Olive and Sassetti 2016). Metabolism includes several
659 components such as glycolysis, gluconeogenesis, citric acid cycle/tricarboxylic acid cycle
660 (TCA), and pentose phosphate pathway (PPP) for carbon metabolism, nitrogen and sulfur
661 metabolisms and oxidative phosphorylation for energy production and nucleotide and amino
662 acid metabolisms (Kanehisa and Goto 2000; Kanehisa *et al.* 2023). The link between
663 metabolism and virulence was recently reviewed using *S. enterica* as a model (Pokorzynski
664 and Groisman 2023). In this section we propose to focus on some metabolic pathways
665 required for bacterial survival into host blood. While specific metabolic pathways have been
666 only studied in a restricted set of bacteria, we will take advantage of the conservation of
667 bacterial metabolism and of the numerous genome-wide screens performed in conditions
668 mimicking bacteremia (see Box 2) to draw conclusions on general metabolic requirements
669 during bloodstream infection, which are summarized in the Supplementary Tables 11, 12, 13
670 and 14.

671

672 **Nucleotide metabolism**

673 Systemic virulence has been linked to nucleotide and related metabolite auxotrophy since
674 the 1950's in bacteria such as *S. enterica* (Bacon, Burrows and Yates 1950, 1951; Gowen *et*
675 *al.* 1953; Formal, Baron and Spilman 1954), *K. pneumoniae* (Garber, Hackett and Franklin
676 1952), *B. pseudomallei* (Levine and Maurer 1958), and later in *B. anthracis* (Ivánovics, Marjai
677 and Dobozy 1968) or *Y. pestis* (Brubaker 1970). *S. enterica* purine-auxotrophic mutants
678 revealed the crucial role in virulence of PurA and PurB, involved in adenosine
679 monophosphate (AMP) biosynthesis from inosine monophosphate (IMP), as well as guanine
680 monophosphate (GMP) biosynthesis proteins GuaA and GuaB, depending on the strain. The
681 role in *S. enterica* virulence of PurC, PurD, PurF, PurG (or PurL) and PurH, involved in IMP

682 biosynthesis, was less pronounced and strain-dependent, suggesting an alternate acquisition
683 or biosynthesis of IMP *in vivo* (McFarland and Stocker 1987), which was previously observed
684 in *B. anthracis* (Ivánovics et al. 1968). A subsequent study on *E. coli* and *S. enterica*
685 uncovered that almost all proteins involved in purine and pyrimidine biosynthesis were
686 required for serum survival (Samant et al. 2008). In the same study, the role of PurE, PurK,
687 CarA and PyrC was investigated in *B. anthracis* vaccine strain Sterne. Interestingly, PurE and
688 PurK were required for bacterial survival in serum but only PurE promoted systemic infection.
689 It was hypothesized that a non-enzymatic reaction at high concentration of bicarbonate could
690 rescue the absence of PurK. *B. anthracis* PurH was later shown to be required for full
691 virulence in guinea pigs but not in other animal infection models (Jenkins et al. 2011).

692 Using random transposon mutagenesis coupled with sequencing, *de novo* biosynthesis
693 genes previously reported in non-pathogenic *E. coli* (Samant et al. 2008) were identified in
694 ExPEC grown in swine serum, and loss of virulence of PurF and PyrF mutants was confirmed
695 in a mouse model of infection (Ma et al. 2021). New screens mostly based on transposon
696 mutagenesis (see box 2 and Supplementary Table 11) further highlighted requirement of
697 nucleotide biosynthetic pathways for bacterial survival in blood or *in vivo* for other bacteria
698 such as in several *Streptococcus* species (Polissi et al. 1998; Le Breton et al. 2013; Hooven
699 et al. 2018; Charbonneau et al. 2020; Zhu et al. 2020, 2021), *Y. pseudotuberculosis*
700 (Crimmins et al. 2012), *Y. pestis* (Palace et al. 2014), *N. meningitidis* (Sun et al. 2000;
701 Mendum et al. 2011; Capel et al. 2017), *P. multocida* (Fuller et al. 2000), *P. mirabilis*
702 (Armbruster et al. 2019), *S. aureus* (Benton et al. 2004; Christiansen et al. 2014; Connolly et
703 al. 2017; Groma et al. 2020), *K. pneumoniae* (Weber et al. 2020) or *E. faecium* (Zhang et al.
704 2017). By combining Tn-Seq with RNA-Seq this latter study pointed out upregulation of
705 expression of the purine biosynthesis operon during bacterial growth in serum.

706 Taken together, these studies highlight the importance of *de novo* biosynthesis of purine
707 and pyrimidine for successful bloodstream infection by a large panel of bacteria, presumably
708 due to low abundance of these molecules in blood. Yet, purin synthesis inactivation was
709 recently shown to enhance complement tolerance in *P. aeruginosa* (see section 'Complement

710 inhibitors'), emphasizing the need to investigate further the role of purin metabolism during
711 infection (Janet-Maitre *et al.* 2023).

712

713 **Amino acid metabolism**

714 Similar to nucleotide auxotrophy, amino acid (AA) auxotrophy was linked to systemic
715 infection several decades ago in *S. enterica* (Bacon *et al.* 1950, 1951). More recent studies,
716 including genome-wide screens, identified bacterial factors involved in biosynthesis or import
717 of amino acid during bacteremia (Supplementary Table 12). The shikimate pathway,
718 responsible for aromatic compound biosynthesis, was targeted via *aroA* and *aroB* mutations
719 to reduce the virulence of *S. enterica* (Hoiseth and Stocker 1981; McFarland and Stocker
720 1987; Günel-Özcan *et al.* 1997; Chaudhuri *et al.* 2009). Virulence of shikimate deficient
721 mutants was so attenuated that they have been used as vaccine candidates against typhoid
722 fever. Further studies showed that this phenotype could be due to a membrane defect in
723 addition to aromatic compound auxotrophy (Sebkova *et al.* 2008). The shikimate pathway has
724 been shown to be involved in bacteremia for multiple bacteria, such as *K. pneumoniae*
725 (Bachman *et al.* 2015; Weber *et al.* 2020), *L. monocytogenes* (Stritzker *et al.* 2004), *S. aureus*
726 (Christiansen *et al.* 2014), several *Streptococcus* species (Hooven *et al.* 2018; Zhu *et al.* 2020),
727 *P. mirabilis* (Armbruster *et al.* 2019), and *N. meningitidis* (Sun *et al.* 2000; Mendum *et al.*
728 2011; Capel *et al.* 2017). The amino acid importer AroP was also shown to be required for
729 optimal systemic infection with *Y. pestis* (Palace *et al.* 2014). Downstream of the shikimate
730 pathway, tryptophan biosynthesis enzymes have been demonstrated as essential for
731 bacterial survival during systemic infection by *S. aureus* (Mei *et al.* 1997; Coulter *et al.* 1998),
732 *N. meningitidis* (Mendum *et al.* 2011; Capel *et al.* 2017) and *Y. pseudotuberculosis* (Crimmins
733 *et al.* 2012). Thus, aromatic compounds seem to be restricted in the bloodstream, and their
734 biosynthesis and/or uptake represent conserved traits of bacteria causing bloodstream
735 infection. Branched-chain amino acids (BCAA), consisting in leucine, isoleucine and valine,
736 were recently described as important for successful systemic infection of several pathogens
737 such as *B. anthracis* (Dutta *et al.* 2022) and *S. aureus* (Kaiser *et al.* 2015). The link between

738 BCAA adaptive response to nutrient fluctuations and regulation of virulence has recently been
739 reviewed (Kaiser and Heinrichs 2018). Various other amino acid metabolic pathways have
740 been shown to be required for successful bloodstream infection. It is well illustrated by the
741 study of *S. aureus* aspartate semialdehyde dehydrogenase Asd, an enzyme required for
742 biosynthesis of lysine, methionine and threonine from aspartate. An Asd-defective mutant, as
743 well as MetE-, ThrC- and LysA-defective mutants, auxotrophs for methionine, threonine and
744 lysine respectively, showed reduced growth in calf serum (Oogai *et al.* 2016). Methionine
745 requirement in blood was also shown by the decreased bacterial survival of methionine
746 transporter deficient strains of *S. agalactiae* (Zhu *et al.* 2020) or *Y. pestis* (Palace *et al.* 2014),
747 and methionine biosynthesis mutants of *N. meningitidis* (Sun *et al.* 2000; Capel *et al.* 2017).
748 Other amino acid-related proteins identified in genome-wide mutational screens in conditions
749 mimicking bacteremia are listed in Supplementary Table 12.

750 The arginine-derived polyamine (putrescine and spermidine) importer PotABCD was
751 shown to be required for pneumococcal septicemia (Polissi *et al.* 1998; Ware *et al.* 2006).
752 The Pot operon and the putrescine biosynthesis enzyme SpeA were found to be required for
753 bloodstream survival in genome-wide mutational screens of *S. aureus* (Groma *et al.* 2020)
754 and *P. mirabilis* (Armbruster *et al.* 2019), respectively. In a mouse model of typhoid fever,
755 polyamines have been shown to be required for expression of *S. enterica* virulence factors
756 and optimal infection (Jelsbak *et al.* 2012).

757 A particular mechanism used by *B. anthracis* to acquire essential amino acids from the
758 host is to proteolyze human hemoglobin, enhancing its growth. This property is mediated by
759 the secreted metalloprotease InhA1 and extends to other serum proteins, including albumin
760 (Terwilliger *et al.* 2015).

761

762 **Carbon metabolism**

763 Carbon metabolism is one of the most fundamental functions in any living organism.
764 Bacteria need to adapt to carbon sources available in the host during infection, in particular
765 in blood (Supplementary Table 13).

766

767 Bacteria acquire carbon from carbohydrate sources available in their environment. They
768 heavily rely on phosphoenolpyruvate-dependent phosphotransferase systems (PTS) which
769 import and phosphorylate carbohydrates. PTS-related proteins important in virulence have
770 been identified in *E. faecium* (Zhang *et al.* 2017), *Y. pestis* (Palace *et al.* 2014) and *N.*
771 *meningitidis* (Sun *et al.* 2000; Capel *et al.* 2017). Surprisingly, the *N. meningitidis* PTS system
772 is incomplete and should not be able to mediate import of carbohydrates. Its contribution to
773 infection could rely on the pleiotropic role of the phosphocarrier protein Hpr during interactions
774 with the host, in particular in blood (Antunes *et al.* 2016a). Mannose- and fructose-specific
775 PTS systems are also required for bloodstream infection with *E. faecium* (Zhang *et al.* 2017)
776 and *S. pyogenes* (Le Breton *et al.* 2013; Valdes *et al.* 2016), highlighting the importance of
777 these specific sugars in blood. Interestingly, growth defect of *S. pyogenes fruR* and *fruB*
778 deletion mutants was observed in human blood and not in mouse blood nor in infected mice,
779 suggesting that fructose PTS are important for *S. pyogenes* survival in a human-specific
780 environment (Valdes *et al.* 2016).

781 Bacteria can also import carbohydrates via ABC transporters or permeases. The non-
782 PTS importer GlcU is required for optimal growth of *S. pyogenes* in blood. While the PtsI-
783 dependent pathway plays a more important role in this phenotype, PTS-dependent and PTS-
784 independent pathways are linked by an unknown mechanism (Sundar *et al.* 2018).
785 Additionally, ExPEC relies on ribose import for its metabolism during bacteremia, but only a
786 double mutant affected in the ribose transporter RbsDACB and in the citrate fermentation
787 system CitCEFXG showed reduced fitness in blood and reduced virulence in infected mice,
788 suggesting a pathway redundancy to support metabolic requirement during infection (Ma *et*
789 *al.* 2020). In *N. meningitidis* the lactate permease LctP is required for resistance to
790 complement (see section 'Complement inhibitors') and bloodstream infection. Interestingly,
791 virulence attenuation of LctP deficient bacteria is mediated through the sialic acid
792 biosynthesis pathway, connecting central carbon metabolism and virulence (Exley *et al.*
793 2005).

794

795 Following import of carbon sources from their environment, bacteria use several
796 pathways such as glycolysis, citrate cycle or the pentose-phosphate pathway to metabolize
797 carbohydrates. These pathways produce energy and synthesize metabolites that directly
798 impact pathogenesis.

799 For example, in addition to the lactate-dependent sialic acid biosynthesis by *N.*
800 *meningitidis* associated to virulence described above, production of the capsule associated
801 to *S. marcescens* virulence relies on phosphoglucomutase Pgm that converts glucose to
802 pyruvate. A Pgm-deficient mutant in *S. enterica* could not use galactose as a carbon source,
803 and showed a defect in LPS biosynthesis as well as virulence attenuation in mice (Chaudhuri
804 *et al.* 2009; Paterson *et al.* 2009). Interestingly, galactose metabolism proteins GalE and GalU
805 have been shown to be required for bacterial resistance to serum and systemic infection (Sun
806 *et al.* 2000; Geoffroy *et al.* 2003; Phan *et al.* 2013; Zou *et al.* 2013; Capel *et al.* 2017), which
807 could be due to their contribution to LPS biosynthesis (Robertson *et al.* 1993; Priebe *et al.*
808 2004). Similarly, the fermentative *S. pneumoniae* requires lactate dehydrogenase Ldh to grow
809 on glucose, survive in blood and promote virulence in mice, possibly through regulation of
810 capsule production (Gaspar *et al.* 2014). In addition, *P. mirabilis* utilizes D-serine as a carbon
811 source during bacteremia upon degradation, which involves DsdA, DsdC and DsdX proteins,
812 (Brauer *et al.* 2019).

813 Carbon metabolic pathways required for successful bloodstream infection are thus
814 diverse. Other examples are available in Supplementary Table 13.

815

816 **Other metabolic pathways**

817 Other metabolic pathways have been found to be required for bacterial survival in blood
818 and/or bloodstream infection using several screens in conditions mimicking bacteremia
819 (Supplementary Table 14).

820 **Electron transport chain.** Several electron transport chain genes have been shown to
821 be required for bacterial survival in blood and virulence. For example, simultaneous deletion

822 of *hybABCD* and *hycEFG*, encoding the Ni-Fe hydrogenases 2 and 3 involved in anaerobic
823 respiratory chains, impairs ExPEC growth in swine blood and in mice (Ma *et al.* 2020). Other
824 electron transport chain components were identified in screens performed in *N. meningitidis*
825 (Capel *et al.* 2017) and *S. enterica* (Chaudhuri *et al.* 2009). However, these studies lacked
826 mechanistic aspects. Conversely, as reported in the section 'Resistance to phagocyte
827 defenses', the electron transport chain sensitized *S. aureus* and *E. faecalis* to neutrophil
828 oxidative burst, and its inactivation led to a greater survival in blood (Painter *et al.* 2017).

829 **Nitrogen metabolism.** Nitrogen is critical for production of amino acids and nucleic
830 acids. Nitrogen assimilation proteins GlnA/GltB, GdhA and NtrB have been shown to be
831 essential for nitrogen acquisition from blood during *P. mirabilis* infection (Armbruster *et al.*
832 2019). Interestingly, orthologous proteins were also identified in other screens of bacterial
833 factors required for survival in blood or *in vivo*, e.g. *S. suis* GlnA (Arenas *et al.* 2020), *E. coli*
834 GltB (McCarthy, Stabler and Taylor 2018) or *N. meningitidis* GdhA (Capel *et al.* 2017). Further
835 studies will be required to better discriminate the relative contribution of these factors to ROS
836 resistance (see section 'Resistance to phagocyte defenses') and nitrogen uptake during
837 bacteremia.

838 **Sulfur metabolism.** As an essential element for life, sulfur needs to be acquired by
839 bacteria from environmental sources such as the abundant cysteine amino acid or its oxidized
840 derivative cystine. It was first observed that the *L. monocytogenes* cysteine importer CtaP
841 was required for systemic virulence, but the pleiotropic effects of its inactivation prevented
842 from drawing any conclusion concerning cysteine requirement (Xayarath *et al.* 2009).
843 Interestingly, proteins involved in cysteine transport (CysA, CysW, CysT) and sulfur
844 metabolism were recently identified as necessary for *N. meningitidis* survival in the
845 bloodstream (Capel *et al.* 2017). Additionally, cysteine/glutathione importer genes *cydCD*
846 were shown to be required for efficient proliferation of *Y. pestis* during systemic infection
847 (Palace *et al.* 2014). In *S. aureus*, regulation of cysteine metabolism plays a central role in
848 stress resistance, host adaptation and virulence (Soutourina *et al.* 2010) and a recent study
849 uncovered the importance of cystine importers TcyP and TcyABC during systemic infection

850 (Lensmire *et al.* 2020). This study concluded that sulfur salvage from host cystine could
851 promote infection, which opens new perspectives on sulfur metabolism at the host-pathogen
852 interface during bacteremia.

853 **Thiamine metabolism.** Thiamine (vitamin B1) is an essential co-factor for aerobic
854 metabolism. Thiamine has been shown to be important for *L. monocytogenes* intracellular
855 lifestyle (Schauer *et al.* 2009), and more recently for *P. aeruginosa* pulmonary infection, as
856 well as being considered a promising target for antimicrobial development (Kim *et al.* 2020).
857 Interestingly, thiamine-related genes were identified in several screens to discover factors
858 involved in bacteremia in various bacteria such as *Y. pestis* (Palace *et al.* 2014), *S. sanguinis*
859 (Zhu *et al.* 2021), *E. faecium* (Zhang *et al.* 2017), *N. meningitidis* (Capel *et al.* 2017), *P.*
860 *mirabilis* (Armbruster *et al.* 2019) and *E. coli* (McCarthy, Stabler and Taylor 2018). However,
861 their precise role during bloodstream infection remains to be addressed.

862 **Biotin metabolism.** Interestingly, while most *in vivo* screens had not identified any biotin-
863 related genes necessary for infection, a recent study highlighted the difference of biotin levels
864 between mice and human blood. In a mouse model mimicking human biotin levels, *A.*
865 *baumannii*, *K. pneumoniae* and *P. aeruginosa* required a biotin biosynthetic pathway for
866 infection (Carfrae *et al.* 2019). The role of biotin metabolism was confirmed in a screen
867 investigating *K. pneumoniae* growth in human plasma (Weber *et al.* 2020). These studies
868 pave the way to new antimicrobial treatments targeting biotin biosynthesis. On the other hand,
869 a recent study suggested that biotin synthesis inactivation in *P. aeruginosa* leads to an
870 enhanced complement resistance (see section 'Complement inhibitors'), highlighting the
871 necessity to investigate further the role of biotin metabolism during bloodstream infection
872 (Janet-Maitre *et al.* 2023).

873 **Bacterial factors mediating adaptive response to blood**

874 Bacteria developed multiple systems for environmental sensing and adaptation. To
875 survive and replicate in the bloodstream, bacteria rely on regulatory mechanisms such as
876 two-component systems, phase variation, small regulatory RNAs, thermosensors, and the
877 stringent response. These mechanisms can promote infection by regulating factors previously
878 described in this review (Figure 8).

879

880 **Two-component systems and phosphorelays**

881 Two-component systems (TCSs) play an important role in sensing the environment that
882 bacteria face during the infection process. TCSs are generally composed of a sensor histidine
883 kinase (SHK) anchored to bacterial surface and a SHK activated-response regulator that acts
884 as a transcriptional activator or repressor of target genes (Jacob-Dubuisson *et al.* 2018).
885 Phosphorelays are a variation of TCSs (Hoch 2000) that differ by having a more complex
886 signal transduction pathway, using additional regulator and phosphotransferase domains. As
887 bacteria reach the bloodstream, they sense signals to adapt rapidly to this environment by
888 deploying mechanisms to subvert the different components of the immune response and
889 adapt their metabolism. In particular, TCSs activate expression of virulence factors important
890 for immune evasion and modulation of biosynthetic pathways (Supplementary Table 15).

891 **Phagocyte subversion.** TCSs allow to sense intracellular environment when bacteria
892 are phagocytosed and trigger a transcriptional program to adapt to the intracellular lifestyle. For
893 example, AgrAC promotes *S. aureus* dissemination in a model of systemic infection by
894 manipulation of the autophagic flux, which could be mediated by the small cytotoxic alpha-
895 helical peptides phenol-soluble modulins (PSMs) (O’Keeffe *et al.* 2015). Interestingly, human
896 serum components, such as apolipoprotein B, downregulate the *agr* operon by sequestering
897 the auto-inducing peptide, which is the trigger of the *agr* quorum sensing circuit. The
898 constitutive expression of the AgrC sensor could overcome this immune response, and
899 naturally occurring mutants in *agrAC* selected by immune pressure could lead to hypervirulent

900 strains (James, Edwards and Wigneshweraraj 2013). Furthermore, to resist to oxidative
901 stress that occurs intra- or extracellularly, the AirSR TCS regulates staphyloxanthin
902 production, which provides antioxidant properties to *S. aureus* and promotes bacterial survival
903 in human blood (Hall *et al.* 2017). Likewise, *P. aeruginosa* superoxide response regulator of
904 the SoxRS TCS is required for resistance to killing mediated by macrophages and systemic
905 infection in a burned mouse model, suggesting protection against oxidative stress (Ha and
906 Jin 1999).

907 Another regulatory mechanism based on phosphorylation is mediated by eukaryotic-like
908 serine/threonine kinases, such as Stk1 in *S. agalactiae* which positively regulates expression
909 of β -haemolysin β -H/C, enhancing resistance to neutrophils and oxidative stress, and
910 possibly expression of the response regulator of the virulence TCS CoyRS (see below)
911 (Rajagopal *et al.* 2006). One of the best characterized intracellular virulence system is the *S.*
912 *enterica* pathogenicity island-2 (SPI-2), its second T3SS. SPI-2 is subjected to a complex
913 regulation. It is primarily activated by the SsrAB TCS (originally known as SpiR/SsrB) located
914 on SPI-2 (Fass and Groisman 2009). SsrAB itself is regulated by other TCSs involved in SPI-
915 2 expression, such as OmpR/EnvZ (Dorman *et al.* 1989; Lee, Detweiler and Falkow 2000)
916 and PhoPQ (Miller *et al.* 1989; Groisman *et al.* 1992; Groisman, Duprey and Choi 2021),
917 promoting infection. Interestingly, inactivation of the TCS kinase PmrA induced a
918 hypervirulent phenotype and the PmrAB TCS repressed SsrAB and SPI-2, which could be a
919 mechanism to induce bacterial persistence (Choi and Groisman 2013). PhoPQ TCS is
920 required for *S. enterica* virulence. It is sensing surface disturbances triggered for example by
921 low Mg^{2+} concentration, acidic pH or AMP encountered intracellularly. PhoPQ regulates SPI-
922 2, Mg^{2+} transport and MgtC-mediated acid resistance, and surface modification promoting
923 resistance to AMP when entering phagolysosomes (Groisman, Duprey and Choi 2021).
924 Interestingly, it was recently reported that the horizontally transferred gene *ssrB* regulates the
925 ancestral PhoPQ, by helping to sense acidic pH through UgtL, thereby promoting infection
926 (Choi and Groisman 2017, 2020; Groisman, Duprey and Choi 2021). Similarly to *S. enterica*

927 PhoPQ, *N. meningitidis* serogroup C PhoPQ promotes resistance to human defensin HNP-1
928 and polymyxin B, bacterial survival in mouse but not human serum, and virulence in mouse
929 model of meningococcal infection (Johnson *et al.* 2001; Newcombe *et al.* 2004). In *N.*
930 *meningitidis* serogroup B, PhoPQ orthologous TCS MisRS, is up-regulated upon exposure to
931 human blood (Echenique-Rivera *et al.* 2011). MisRS promotes resistance to oxidative stress,
932 but decreases capsule production and resistance to bactericidal activity in human serum
933 (Tzeng *et al.* 2008).

934 **Envelope modification and complement subversion.** TCS are widely used to regulate
935 surface modification at the host-pathogen interface, reinforcing the envelope and promoting
936 evasion from complement killing.

937 Capsule or extracellular polysaccharide (EPS) production is often controlled by TCSs,
938 such as *S. pneumoniae* ZmpRS, linking carbon metabolism, capsule production and infection
939 (Hirschmann *et al.* 2021a, 2021b). Other examples are *A. baumannii* BfmRS involved in
940 production of capsular EPS upon bacterial exposure to low concentrations of antibiotics
941 (Geisinger and Isberg 2015) and ExPEC TCS Rcs which controls EPS colanic acid production
942 (Miajlovic and Smith 2014). Similar to TCS, eukaryotic-like serine/threonine kinase and
943 phosphatase Stk and Stp1 of *S. suis* regulate capsule thickness and virulence factors
944 promoting virulence (Liu *et al.* 2021). In *S. pyogenes*, CovRS regulates virulence factors
945 involved in complement resistance in a strain-dependent manner (Sugareva *et al.* 2010).

946 LOS modification can also be regulated by TCSs. *H. influenzae* oxygen-dependent ArcAB
947 TCS modulates expression of *lic2B*, a gene encoding a glycosyltransferase required for
948 addition of a galactose residue to the outer core of LOS, promoting resistance to the
949 complement classical pathway in serum and bacteremia in mice (De Souza-Hart *et al.* 2003;
950 Wong *et al.* 2011). Interestingly, using genetic screens, ArcAB was also found to be required
951 for bloodstream infection with *S. marcescens* (Anderson *et al.* 2017) and *C. freundii*
952 (Anderson *et al.* 2018). These studies suggest a conserved role of this TCS in bacterial
953 survival in blood. While LPS restructuring regulated by TCS such as PhoPQ or PmrAB has
954 been described in *S. enterica* (Groisman *et al.* 2021), implication of these modifications in

955 bloodstream infection remains to be established.

956 TCSs also regulate proteins involved in complement subversion. For example, *P.*
957 *aeruginosa* PhoPQ has been shown to downregulate the expression of OprH, a protein that
958 binds complement factor C3, thus subverting opsonophagocytosis and promoting bacterial
959 survival in blood and thereby infection (Qadi *et al.* 2017). Similarly, *S. mutans* VicRK TCS has
960 been linked to the regulation of PepO, a peptidase also involved in reduction of C3b
961 deposition and serum killing (Alves *et al.* 2017). In *S. aureus*, AirSR is necessary for
962 expression of proteases SspA, SspB and SspC, cleaving C3 and allowing complement and
963 phagocytosis escape (Hall *et al.* 2015). Lastly, *S. suis* WalRK TCS is involved in resistance
964 to phagocytosis and virulence in mice, possibly by regulating expression of the gene encoding
965 HP1065, a homolog of *S. pneumoniae* PspA, which plays a role in complement resistance
966 (Pei *et al.* 2020). Surprisingly, while *Y. enterocolitica* OmpR/EnvZ regulates the complement
967 resistance proteins Ail and OmpX, a strain lacking OmpR exhibits extremely high resistance
968 to the bactericidal activity of serum. It has been proposed that OmpR could sensitize bacteria
969 to complement killing by remodeling the outer membrane, altering the function of the major
970 serum resistance factor YadA and the levels of the flagellar activator FlhDC (Skorek *et al.*
971 2013).

972 **Coagulation.** Some bacteria use TCSs to regulate factors subverting the coagulation
973 process. SaeRS, whose expression is upregulated upon *S. aureus* exposure to human blood
974 (Malachowa *et al.* 2011), has been shown to contribute to bacterial survival in human blood
975 and virulence in an *in vivo* model (Voyich *et al.* 2009). Conversely, a recent study reported
976 that SaeRS regulates the coagulase Coa, a protein able to convert host prothrombin to
977 staphylothrombin, leading to activation of the protease activity of thrombin and localized
978 clotting detrimental to *S. aureus* survival in the bloodstream. This discrepancy has been
979 hypothesized to be due to the variability in blood samples from different donors and/or
980 differences in growth phase of bacteria inoculated (Guo *et al.* 2017). Another *S. aureus* TCS,
981 ArIRS, has been shown to be involved in the regulation of agglutination during exposure to
982 human plasma or fibrinogen and to affect the bacteremic phase of infection. This agglutination

983 phenotype is due to the negative regulation of the giant staphylococcal surface protein
984 (GSSP) preventing fibrinogen binding and bacterial clumping (Walker *et al.* 2013). It was later
985 shown that ArIRS promotes the expression of the redox-sensitive virulence regulator MgrA,
986 enhancing leucocidin or capsule expression and decreasing GSSP and other surface protein
987 expression (Crosby *et al.* 2016, 2020).

988

989 **Transcriptional regulators**

990 Transcriptional regulators (TRs) control gene expression, including that of virulence
991 determinants (Balleza *et al.* 2009). Several transcriptional regulators playing a role in the
992 bacteremic phase of infection have been identified (Supplementary Table 16). Major
993 regulatory mechanisms are described below.

994 **Nutritional immunity.** Iron metabolism, involving iron transport and storage, is
995 generally regulated by the repressor Fur or Fur homologues upon binding ferrous iron. The
996 role of Fur in subversion of nutritional immunity in blood was identified in *N. meningitidis*
997 (Echenique-Rivera *et al.* 2011) and in ExPEC (Huja *et al.* 2014; Ma *et al.* 2021). In *V.*
998 *vulnificus* the global regulator Lrp positively regulates expression of genes involved in iron
999 acquisition and secretion of the MARTX cytotoxin, promoting bacterial survival in serum and
1000 cytotoxicity (Ho *et al.* 2017). In *S. pneumoniae* the iron-dependent transcriptional regulator
1001 IDTR regulates transcription of several genes involved in virulence and iron metabolism, and
1002 is required for full virulence in a mouse model of sepsis (Gupta *et al.* 2013).

1003 Similar to Fur, the manganese-cofactored MntR has been shown to be required for
1004 systemic infection. In *S. aureus*, MntR regulates manganese homeostasis through the control
1005 of MntABC transporter and MntE exporter (Grunenwald *et al.* 2019). *S. aureus* virulence also
1006 relies on the LysR-type transcriptional regulator LTTR, which controls expression of the
1007 copper detoxification transporter CopA (Groma *et al.* 2020).

1008 Interestingly, a new regulatory mechanism based on sensing amino acid content of
1009 phagocytes was recently described. *S. enterica mgtCB* operon transcription, required for Mg²⁺
1010 transport and resistance to acidic pH of the phagolysosome, relies on the upstream proline

1011 codon-rich *mgtP* sequence, which allows translation in absence of proline-charged tRNA^{Pro}
1012 in response to proline limitation (Lee et al. 2014).

1013 **Metabolism.** Regulation of amino acid and nucleotide metabolism is crucial for bacterial
1014 proliferation in the bloodstream. *S. aureus* LTTR previously mentioned was recently shown
1015 to be required for efficient colonization in a metastatic bloodstream infection model. LTTR
1016 positively regulates amino acid biosynthesis and transport genes and decreases transcription
1017 of genes involved in nucleotide biosynthesis and PTS transport (Groma *et al.* 2020).
1018 Additionally, the master regulator of cysteine metabolism CymR also promotes *S. aureus*
1019 survival in macrophages and in a mouse model of infection, presumably by regulating genes
1020 involved in response to oxidative stress and metal ion homeostasis (Soutourina *et al.* 2010).
1021 Furthermore, *S. agalactiae* MrvR, a transcription factor of the GntR family, controls the
1022 expression of genes involved in nucleotide biosynthesis and salvage pathways and is
1023 required for full virulence in a sepsis model (Dammann *et al.* 2021). The LysR family
1024 transcriptional regulator CpsY is important for streptococcal fitness in blood, but its regulatory
1025 effect on methionine metabolism depends on the species, preventing to draw a general
1026 conclusion on its exact mode of action (Allen and Neely 2011; Le Breton *et al.* 2013).

1027 ExPEC FNR, involved in adaptation to anaerobic lifestyle and controlling central
1028 metabolic processes, is required for survival in blood and infection (Ma *et al.* 2020, 2021),
1029 highlighting the need of metabolic adaptation to survive and proliferate in the bloodstream.
1030 Likewise, *N. meningitidis* HexR was identified as a repressor that can affect expression of
1031 central carbon metabolism genes in presence of glucose and required to establish bacteremia
1032 in an infant rat model (Antunes *et al.* 2016b). *S. pyogenes* RofA-like protein regulator type 3,
1033 Ralp3, a central regulator of the ERES pathogenicity island, contributes to hyaluronic acid
1034 capsule production and bacterial survival in human blood and serum. Comparative
1035 transcriptomic analysis of wild type and *ralp3* mutant strains showed differential use of carbon
1036 sources which could contribute to capsule synthesis, effects that were specific to serotypes
1037 (Siemens *et al.* 2012). These examples highlight the importance of tight regulation of bacterial
1038 metabolism to adapt and proliferate in the bloodstream.

1039 **Capsule, LPS and surface components regulation.** Surface components involved in
1040 bloodstream infection, such as LPS or capsule, which allow resistance to complement, AMP
1041 and phagocytes, are tightly controlled. For example, HyxA and HyxR are modulators of O-
1042 antigen in UPEC (Phan *et al.* 2013) and presumably promote resistance to complement also
1043 in ExPEC (Ma *et al.* 2021). Another regulatory mechanism is exemplified by RfaH
1044 antiterminator that controls bacterial surface structure by regulating expression of operons
1045 that direct biosynthesis, assembly, and export of LPS core components, pili, and capsule in
1046 addition to toxins. This regulation promotes bacterial survival in blood in *E. coli* (McCarthy,
1047 Stabler and Taylor 2018), *K. pneumoniae* (Bachman *et al.* 2015) and *V. vulnificus* (Garrett *et*
1048 *al.* 2016). The latter study also highlights the role of RfaH-mediated phase variation for
1049 capsule production. UPEC MrpA and LrhA also regulate capsule production, positively and
1050 negatively, respectively, a mechanism which is conserved among different strains and
1051 capsule types (Goh *et al.* 2017). A combination of gradient centrifugation and TRADIS
1052 (TRADIsort) in *K. pneumoniae* also identified MprA as a capsule regulator (Dorman *et al.*
1053 2018) necessary for serum survival (Bachman *et al.* 2015). KbvR is another capsule regulator
1054 which also influences OMPs production and participates in *K. pneumoniae* resistance to
1055 serum, AMPs and phagocytic killing, thus promoting systemic infection (Xu *et al.* 2021).

1056 Interestingly, *Y. pestis* fimbriae PsaA required for septicemic plague, is only produced at
1057 37°C and at pH 6 (Lindler, Klempner and Straley 1990). The mechanism of its regulation by
1058 the transcriptional regulator PsaE, also required for systemic infection, was recently
1059 deciphered and consists in several layers of post-transcriptional and post-translational
1060 regulation. An RNA thermosensor (see below) controls translation of both PsaE and PsaF, a
1061 histidine-rich pH sensor stable at low pH. PsaF is required to prevent PsaE degradation,
1062 which can in turn transcribe PsaA (Quinn *et al.* 2019; Li *et al.* 2021; Quinn *et al.* 2021).

1063 **Other virulence determinants.** Using *in vivo* induced antigen technology (IVIAT) in
1064 convalescent-phase human serum, the transcriptional regulator HlyU was identified to be one
1065 of the master regulators of *V. vulnificus* virulence. HlyU controls production of the
1066 hemolysin/cytolysin VvhA and the elastolytic protease. The identification of *hlyU* by IVIAT

1067 suggests the importance of this gene in the bloodstream phase of infection (Kim *et al.* 2003).
1068 Recently the virulence regulator Rsp has been shown to play a role in *S. aureus* transition
1069 from the colonizing stage to the bacteremic stage. This regulator modulates activity of the
1070 transcriptional regulator Agr, leading to opposite effects on bacterial survival in blood and
1071 antibiotic susceptibility (Krishna *et al.* 2018).

1072 In *S. enterica*, expression of SPI-2 associated genes is regulated by the transcription
1073 factor SlyA of the MarR family (Libby *et al.* 1994; Linehan *et al.* 2005; Yoon *et al.* 2009; Banda
1074 *et al.* 2019), as well as IHF (HimD) and RpoE (Fass and Groisman 2009; Osborne and
1075 Coombes 2009; Yoon *et al.* 2009). SlyA also induces expression of *ssrAB*, thereby promoting
1076 virulence. Strikingly, RovA, the homologue of SlyA in *Yersinia* spp. plays a limited role in
1077 systemic infection (Dube *et al.* 2003; Cathelyn *et al.* 2006), which could be explained by the
1078 diversification of their respective regulons (Will *et al.* 2019).

1079

1080 **Phase variation**

1081 An additional mechanism of regulation of gene expression in bacteria is phase variation.
1082 Phase variation refers to the mechanism by which bacteria regulate the expression of certain
1083 groups of genes rapidly and in a reversible manner, either by on-off switching or by
1084 modulating the expression of multiple allelic variants (Van Der Woude and Bäumlér 2004).
1085 The presence of phase-variable genes allows to generate phenotypically diverse populations
1086 of variants, some of which may be better suited to either colonize certain host niches, survive
1087 in a particular environment and/or evade immune responses. Genes under phase-variable
1088 control typically encode bacterial surface structures important for host adaptation such as
1089 those playing a role in bloodstream infection, e.g. adhesins, pili, capsule and LOS
1090 (Supplementary Table 17).

1091 **LPS/LOS.** An example of phase variation contributing to resistance to innate immune
1092 response in the bloodstream is regulation of LOS modification by phosphorylcholine (PCho)
1093 in *H. influenzae*. PCho is acquired from the host through the *lic* operon, which is controlled
1094 by phase variation. It has been suggested that this mechanism decreases the amount of C3

1095 deposition on bacterial surface, thereby increasing survival in serum (Langereis *et al.* 2019).

1096 In *S. enterica* serovar Typhi, the O-antigen side chain of the LPS can be modified by the
1097 activity of the glucosyltransferase *gtr* operons. The glucosylated form of the O-antigen
1098 enhances bacterial survival in human serum by decreased complement binding. Expression
1099 of the *gtrC* gene is controlled by epigenetic phase variation. It has been described that a
1100 single nucleotide deviation from an epigenetic phase variation signature sequence leads to
1101 uniform expression of the *gtr* operon in the population. (Broadbent *et al.* 2010).

1102 In *N. gonorrhoeae* the regulation of *lptA*, involved in phosphoethanolamine (PEA)
1103 decoration of LOS lipid A, has been proposed to be under phase variation. High-frequency
1104 mutations in a polynucleotide repeat within *lptA* can translate into a stop codon and
1105 consequently an on/off switch, influencing gonococcal resistance to cationic antimicrobial
1106 peptides (Kandler *et al.* 2014).

1107 **Capsule.** In *N. meningitidis*, the most frequent change in serogroup B strains is phase
1108 variation of the gene *siaD*, which encodes the sialyl transferase involved in capsule synthesis.
1109 Other genes in sialic acid biosynthesis or export of the capsule can be inactivated by
1110 transposition of the insertion sequence IS1301 (Hammerschmidt *et al.* 1996). It has been later
1111 shown in *N. meningitidis* serogroup C that the insertion of IS1301 into the *sia/ctr* intergenic
1112 region leads to upregulation of capsule expression and enhanced resistance against
1113 complement-mediated lysis. Insertion and excision of IS1301 into *siaA* causes phase-
1114 variation of capsule biosynthesis that most likely occurs *in vivo* during bacteremia (Uria *et al.*
1115 2008).

1116 In *S. pneumoniae* phase variation regulates capsule polysaccharide and teichoic acid
1117 production. More capsular polysaccharide and less teichoic acid translate into increased
1118 virulence. In this context, survival in the bloodstream may be promoted (Kim and Weiser
1119 1998). Furthermore, modulation of the capsule in *S. pneumoniae* can be regulated by tandem
1120 duplications within the *cap3A* gene of the type 3 capsule locus. The transition between the
1121 off (duplication) and on (no-duplication) states depends on reversion of the duplication (Waite,
1122 Struthers and Dowson 2001). Although this phase variation mechanism has not been

1123 demonstrated *in vivo*, it could play a role during the bacteremic phase of infection.

1124

1125 **Small RNAs**

1126 Small RNAs are ubiquitous regulators in the three domains of life. Bacteria employ small
1127 RNAs ranging from 50 to 500 nucleotides for posttranscriptional regulation. These sRNAs
1128 fold into diverse structures and act on gene targets with different molecular mechanisms. One
1129 of the major mechanisms of sRNA-mediated regulation in bacteria is direct binding of the
1130 sRNA via base pairing to a target mRNA. A single sRNA can play a central regulatory role in
1131 controlling multiple gene targets leading to a global regulatory effect. Regulation mediated by
1132 sRNA provides a fast mechanism for bacterial adaptation to environmental stress (Gottesman
1133 and Storz 2011) (Supplementary Table 17).

1134 **Metabolism.** ArcAB TCS has been shown to downregulate expression of sRNA-17 to
1135 promote *E. coli* K1 survival in blood and crossing of the blood-brain barrier. Functional
1136 analysis using a bacteremia mouse model showed that sRNA-17 deletion promotes survival
1137 in the blood, possibly by increasing the expression of genes involved in amino acid transport
1138 and metabolism (Sun *et al.* 2020). In *N. meningitidis*, a tiling microarray analysis of bacteria
1139 grown in human blood allowed identification of several differential expressed sRNAs. Four
1140 sRNAs promoted bacteremia when tested in an infant rat model of bacteremia. One sRNA
1141 designated Bns1 is linked to a GntR-like regulator and belongs to a network that responds to
1142 carbon source availability and energy metabolism important for blood survival (Fagnocchi *et*
1143 *al.* 2015). In *S. pneumoniae*, the F41 sRNA promotes survival in blood in a sepsis infection
1144 model, which could be due to the regulation of a putative ABC transporter involved in
1145 carbohydrate transport.

1146 **Capsule and surface components.** *S. pyogenes* Mga-activating regulatory sRNA
1147 (MarS) positively regulates capsule production and the multiple virulence gene regulator *mga*,
1148 controlling expression of the *emm* gene encoding the antiphagocytic protein M. Deletion of
1149 this small RNA has been shown to decrease bacterial survival in human blood that could be
1150 related to the lack of M protein and susceptibility to neutrophil clearance. Additionally, the

1151 *marS* mutant had reduced virulence in a mouse infection model. This sRNA is conserved in
1152 many streptococci and could be a mechanism of gene regulation shared by different
1153 *Streptococcus* species (Pappesch *et al.* 2017).

1154 **Coagulation.** *S. pyogenes* FasX sRNA negatively regulates the expression of pili and
1155 positively regulates the thrombolytic agent streptokinase, in a serotype dependent manner.
1156 Inactivation of FasX increases expression of pili and decreases expression of streptokinase
1157 that catalyzes activation of human plasminogen into plasmin which can process several
1158 enzymes to degrade blood clots and activate metalloproteinases and collagenases. FasX
1159 promotes virulence in a bacteremia model of mice expressing human plasminogen (Danger
1160 *et al.* 2015).

1161

1162 **Thermosensors**

1163 Thermosensors include bacterial DNA, RNA and proteins that can control gene
1164 expression in response to changes in environmental temperature. Some RNA thermometers
1165 (RNATs), which consist of RNA loops blocking access to the ribosome at low temperature
1166 (Loh *et al.* 2018), have been shown to control gene expression of bacteria during the
1167 bacteremic phase of infection (Supplementary Table 17).

1168 *N. meningitidis* regulates expression of the capsule gene *cssA*, the LPS sialylation gene
1169 *Ist* and *fHbp* by RNATs. These three factors are important for evasion of immune killing and
1170 contribute to proliferation in the bloodstream (Loh *et al.* 2013). A recent report based on
1171 comparative analysis of the promoter regions of *fHbp* suggests that only some *fHbp* alleles
1172 undergo thermoregulation and that the levels of expression of fHbp may be regulated by
1173 variation in the coding sequence of the open reading frame (Spinsanti *et al.* 2021). Other
1174 RNATs regulate expression of capsule and factor H binding proteins in *S. pneumoniae* and
1175 *H. influenzae* (Eichner *et al.* 2021), thereby modulating resistance to complement.

1176 Another well-known thermo-regulated virulence factor is the T3SS of pathogenic *Yersinia*
1177 species whose expression is induced at 37°C. It has been shown that the main T3SS
1178 regulator LcrF is under the combined regulation of an RNAT in the 5' untranslated region

1179 (UTR) and of the thermolabile regulator YmoA (Böhme *et al.* 2012). LcrF is upregulated upon
1180 *Y. pseudotuberculosis* incubation in human plasma (Rosso *et al.* 2008), but the effect of the
1181 RNAT was only assessed in an intestinal infection model and would require further
1182 investigation in a systemic infection model. The transcriptional regulator PsaE, regulating the
1183 production of the *Y. pestis* PsaA fimbriae mentioned above, is also under control of an RNAT
1184 (Quinn *et al.* 2019; Li *et al.* 2021).

1185 *S. enterica* TviA regulator is also under the control of an RNAT located in its 5' UTR. TviA
1186 regulates virulence factors such as the Vi capsule, and its RNAT is required for innate immune
1187 evasion (Brewer *et al.* 2021).

1188 While the first thermosensors were described 20 years ago and other reports identified
1189 important virulence factors under control of RNATs, further studies are needed to gain a better
1190 understanding of RNATs implication during bloodstream infection.

1191

1192 **Stringent response**

1193 Blood is a harsh environment challenging bacterial survival and triggering the stringent
1194 response (SR) (Supplementary Table 17). Stringent response is defined by global changes
1195 in bacterial gene expression associated with nutritional deprivation. The SR is triggered by
1196 intracellular accumulation of two small, hyperphosphorylated GTP-/GDP-derived molecules,
1197 namely, pppGpp and ppGpp, collectively designated (p)ppGpp or alarmones (Irving *et al.*
1198 2020).

1199 **SR-regulated surface structures.** SR is generally mediated by (p)ppGpp synthetase
1200 RelA and (p)ppGpp synthetase/hydrolase SpoT. Deletion of *relA* and *spoT* in *S. enterica*
1201 serovar Typhi induces a (p)ppGpp₀ phenotype, and affects Vi capsule expression, resistance
1202 to complement and survival in macrophages (Dasgupta *et al.* 2019). More recently, SpoT and
1203 the nucleotide hydrolase PpnN target of SR were shown to change the structure of *S. enterica*
1204 O-antigen and contribute to resistance to complement and survival in human serum (Chau *et*
1205 *al.* 2021).

1206 In *E. coli* K1, expression of the (p)ppGpp activated sigma factor RpoE is significantly

1207 increased in the bloodstream and inactivation of this stress sigma factor leads to lower level
1208 of bacteremia in a mouse model of infection. RpoE directly regulates expression of some
1209 virulence genes such as *ompA*, *cnf1*, *fimB*, *ibeA*, and the capsule genes *kpsM*, and *kpsF*.
1210 Also, RpoE indirectly modulates some virulence genes such as *fimA*, *aslA*, and *traJ* (Fan *et*
1211 *al.* 2022). This example shows the broad impact of SR on regulation of virulence during
1212 bacteremia.

1213 **Metabolic requirements for the SR.** The study of methicillin-resistant *S. aureus*
1214 (MRSA) strains causing persistent or resolving bacteremia revealed a connection between
1215 purine biosynthesis pathways and SR. MRSA strains causing persistent bacteremia had
1216 significantly higher (p)ppGpp production, showed increased survival and induced higher lysis
1217 of neutrophils, and expressed higher levels of phenol-soluble modulins Psm α 1–4. A *purF*
1218 deletion mutant produced less GDP, GTP and consequently less (p)ppGpp, linking the purine
1219 biosynthesis pathway to SR. Additionally, a mutant of *relP* encoding another alarmone
1220 synthetase exhibits decreased Psm α 1–4 and Psm β 1,2 expression, reduced neutrophil lysis
1221 and decreased MRSA survival in neutrophils. Importantly, the *relP* gene has been
1222 demonstrated to be necessary to overcome antibiotic treatment in persistent MRSA
1223 bacteremia isolates (Li *et al.* 2020).

1224 These examples highlight the connection between SR and bacterial survival in blood and
1225 the complexity of this adaptative mechanism. Recently, the importance of *A. baumannii* SpoT
1226 during infection was uncovered by a proteomic analysis comparing bacterial infection of
1227 macrophages in absence of presence of polymyxin B. This type of study emphasizes the
1228 importance of deciphering the complex tripartite interactions between bacteria, their host, and
1229 antibiotics to optimize the use of antimicrobials and develop innovative therapies against
1230 multidrug-resistant pathogenic microorganisms (Kho *et al.* 2022).

1231 **Conclusion**

1232 Bacterial infection of the bloodstream is a serious threat that has become an important
1233 global health issue in the context of antibiotic resistance. Characterization of mechanisms
1234 involved in bacterial survival and proliferation in blood could help to develop alternative
1235 therapeutic strategies. The genomic revolution has enabled us to explore these mechanisms
1236 on a large scale, first with sequencing of bacterial genomes and later with functional
1237 approaches based on transcriptomics, proteomics and transposon mutagenesis. Application
1238 of functional genomics resulted in identification of a wealth of bacterial factors important for
1239 survival in blood. In addition, combination of high-throughput approaches with relevant *ex*
1240 *vivo* and *in vivo* experimental models led to a more comprehensive understanding of the
1241 bacteremic phase of infectious diseases.

1242 An overview of research investigating pathogenesis of a broad-range of blood-borne
1243 pathogenic bacteria highlights a striking conservation of host defense subversion
1244 mechanisms, e.g. by targeting components of the complement pathways. Yet, other
1245 mechanisms have been evolved specifically by specific species and even by specific strains
1246 elucidating unique pathogenic properties of some clinical isolates. Bloodstream being a highly
1247 complex and dynamic environment, the multiple regulatory mechanisms evolved by
1248 pathogenic bacteria to evade host immunity and adapt to nutritional restrictions are
1249 expectedly extremely complex systems whose activation signals and crosstalks remain to be
1250 fully deciphered. Resistance to antibiotic treatment leading to development of subpopulations
1251 of bacteria, such as evaders and persisters, adds another layer of complexity in the study of
1252 host-pathogen interactions in bloodstream infections.

1253 Remarkable progress has been made in recent years toward an unprecedented
1254 meticulous characterization of infection biology due to convergence of technologies such as
1255 single-cell transcriptomics, dual proteomics, live cell imaging, tissue bioengineering, genome
1256 editing and machine learning. Application of these innovative technologies to the study of
1257 bloodstream infection will empower us to understand and predict highly complex host-

1258 pathogen interactions, and ultimately help design next-generation diagnostics, vaccines and
1259 drugs in our post-antibiotic era.

1260

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1273

1274

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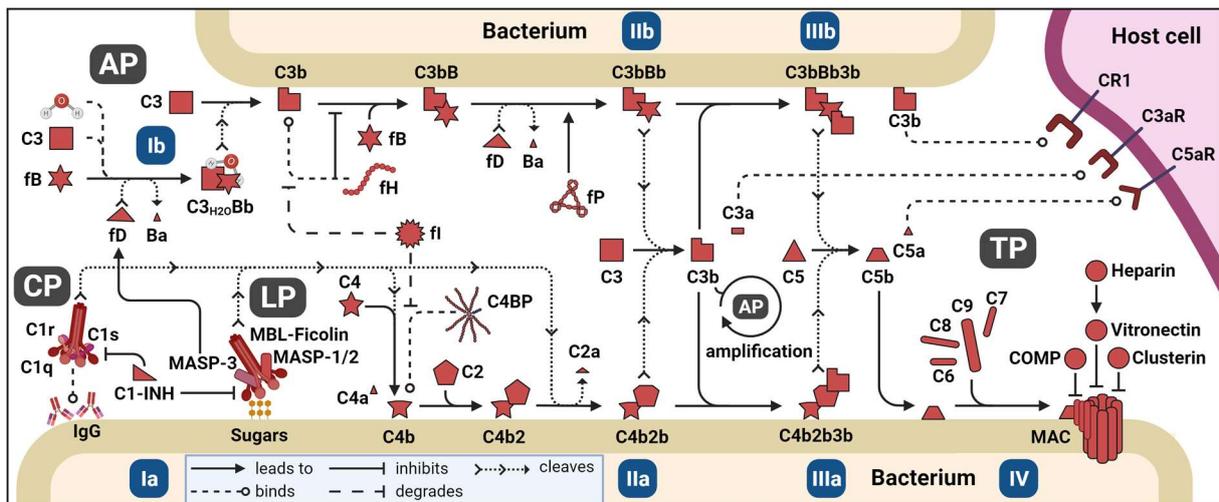


Figure 1.

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Figure 1. The complement pathways. The classical pathway (CP) and lectin pathway (LP) are activated by binding to immunoglobulins and carbohydrate patterns, respectively (Ia). The alternative pathway (AP) is activated by the soluble C3 convertase $C3H_2O Bb$ (Ib) or serves as amplification loop for the three pathways. The downstream cascades both lead to the formation of C3 convertases, converting C3 in C3a and C3b: C4b2b for the CP and LP (IIa) and C3bBb for the AP (IIb). Enrichment in C3b leads to the formation of C5 convertases, converting C5 in C5a and C5b: C4b2b3b for the CP and LP (IIIa) and C3bBb3b for the AP (IIIb). C5b deposition activates the terminal pathway (TP) consisting in C6-C9 recruitment and membrane attack complex formation (IV). Abbreviations: C1-INH: C1-inhibitor. C3aR: C3a receptor. C4BP: C4-binding protein. C5aR: C5a receptor. COMP: cartilage oligomeric matrix protein. CR1: complement receptor 1. fB: factor B. fD: factor D. fH: factor H. fI: factor I. fP: factor P (properdin). IgG: immunoglobulin G. MAC: membrane attack complex. MASP: mannose-binding lectin-associated protease. MBL:mannose-binding lectin.

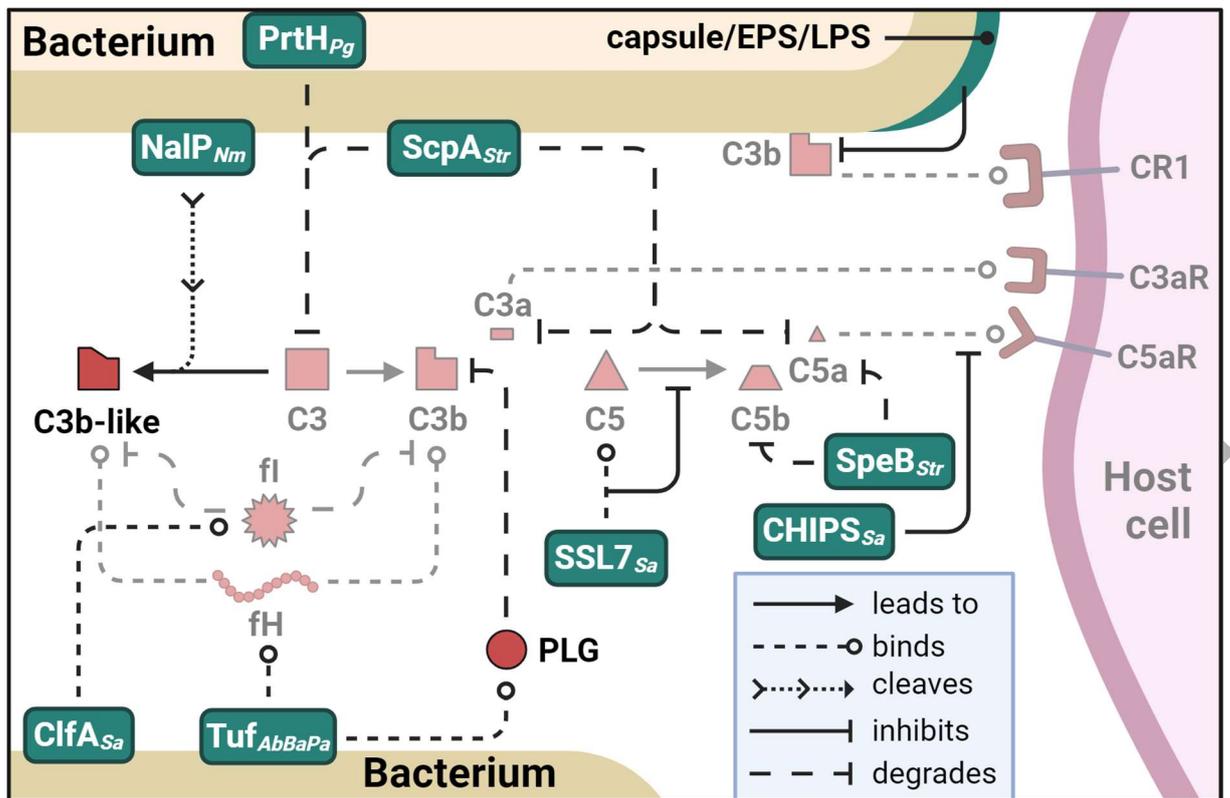


Figure 2.

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Figure 2. Examples of bacterial factors (green) targeting common components of the complement pathways (red). Factors involved in host subversion are displayed at the foreground. Bacterial species: *Ab*: *Acinetobacter baumannii*. *Ba*: *Bacillus anthracis*. *Nm*: *Neisseria meningitidis*. *Pa*: *Pseudomonas aeruginosa*. *Pg*: *Porphyromonas gingivalis*. *Sa*: *Staphylococcus aureus*. *Str*: *Streptococcus* species. Abbreviations: C3aR: C3a receptor. C5aR: C5a receptor. CR1: complement receptor 1. EPS: exopolysaccharide. fh: factor H. fl: factor I. LPS: lipopolysaccharide. PLG: plasminogen.

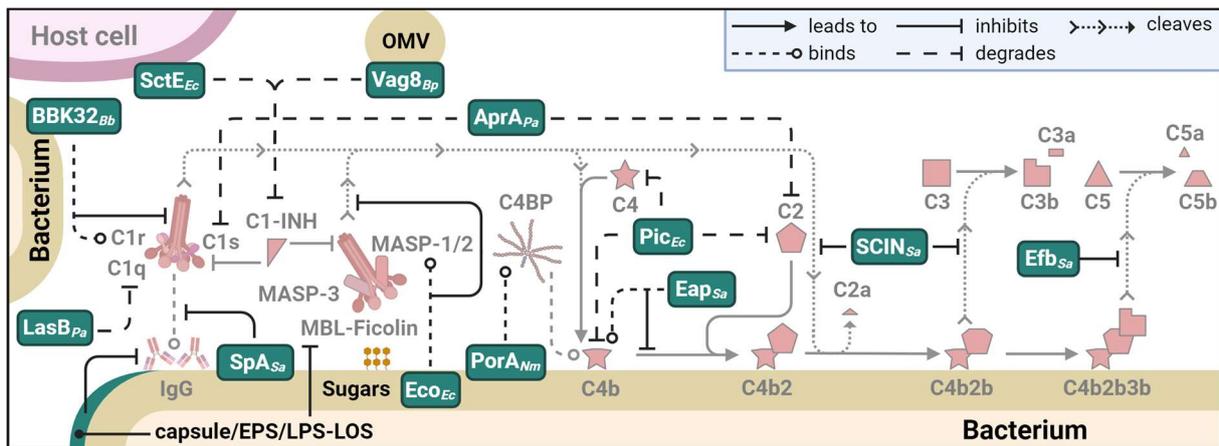


Figure 3.

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2390 **Figure 3.** Examples of bacterial factors (green) targeting host components (red) of the
 2391 classical and lectin pathways. Factors involved in host subversion are displayed at the
 2392 foreground. Bacterial species: *Bb*: *Borrelia burgdorferi*. *Bp*: *Bordetella pertussis*. *Ec*:
 2393 *Escherichia coli*. *Nm*: *Neisseria meningitidis*. *Pa*: *Pseudomonas aeruginosa*. *Sa*:
 2394 *Staphylococcus aureus*. Abbreviations: C4BP: C4-binding protein. EPS:
 2395 exopolysaccharide. IgG: immunoglobulin G. LOS: lipooligosaccharide. LPS:
 2396 lipopolysaccharide. MASP: mannose-binding lectin-associated protease. MBL:
 2397 mannose-binding lectin. OMV: outer membrane vesicle.

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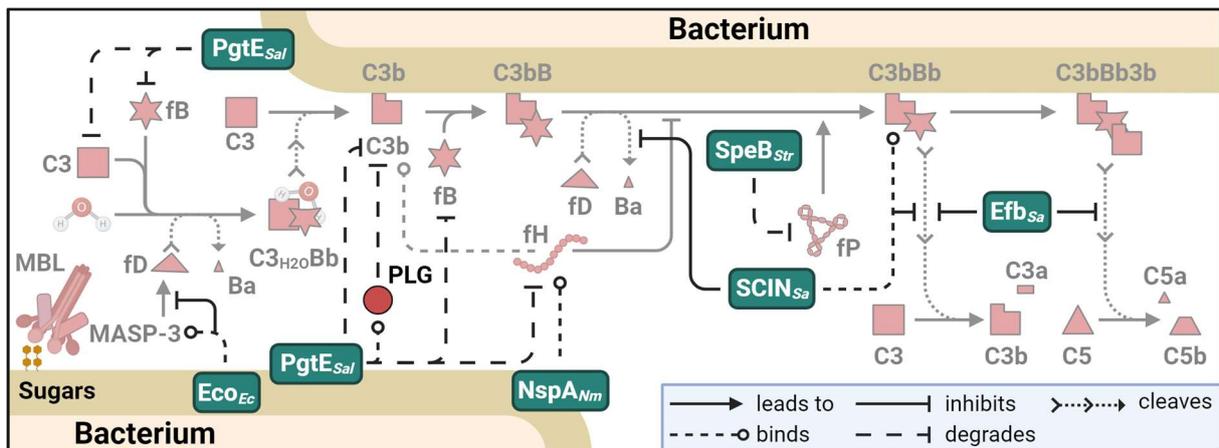


Figure 4.

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2401 **Figure 4.** Examples of bacterial factors (green) targeting host components (red) of
 2402 the alternative pathway. Factors involved in host subversion are displayed at the
 2403 foreground. Bacterial species: *Nm*: *Neisseria meningitidis*. *Sa*: *Staphylococcus aureus*.
 2404 *Sal*: *Salmonella* species. *Str*: *Streptococcus* species. Abbreviations: fB: factor B. fD: factor
 2405 D. fH: factor H. fP: factor P (properdin). MASP: mannose-binding lectin-associated
 2406 protease. MBL: mannose-binding lectin. PLG: plasminogen.

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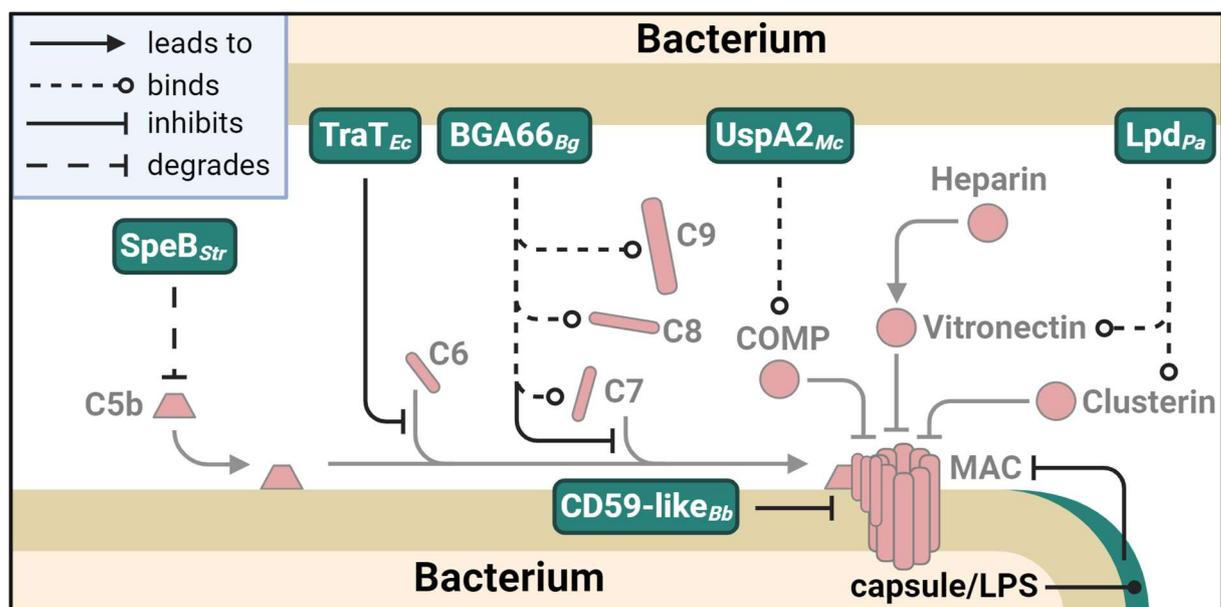


Figure 5.

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2410 **Figure 5.** Examples of bacterial factors (green) targeting host components (red) of
 2411 the terminal pathway. Factors involved in host subversion are displayed at the foreground.

2412 Bacterial species: *Bb*: *Borrelia burgdorferi*. *Bg*: *Borrelia garinii*. *Ec*: *Escherichia coli*. *Mc*:
 2413 *Moraxella catarrhalis*. *Pa*: *Pseudomonas aeruginosa*. *Str*: *Streptococcus* species.

2414 Abbreviations: COMP: cartilage oligomeric matrix protein. LPS: lipopolysaccharide. MAC:
 2415 membrane attack complex.

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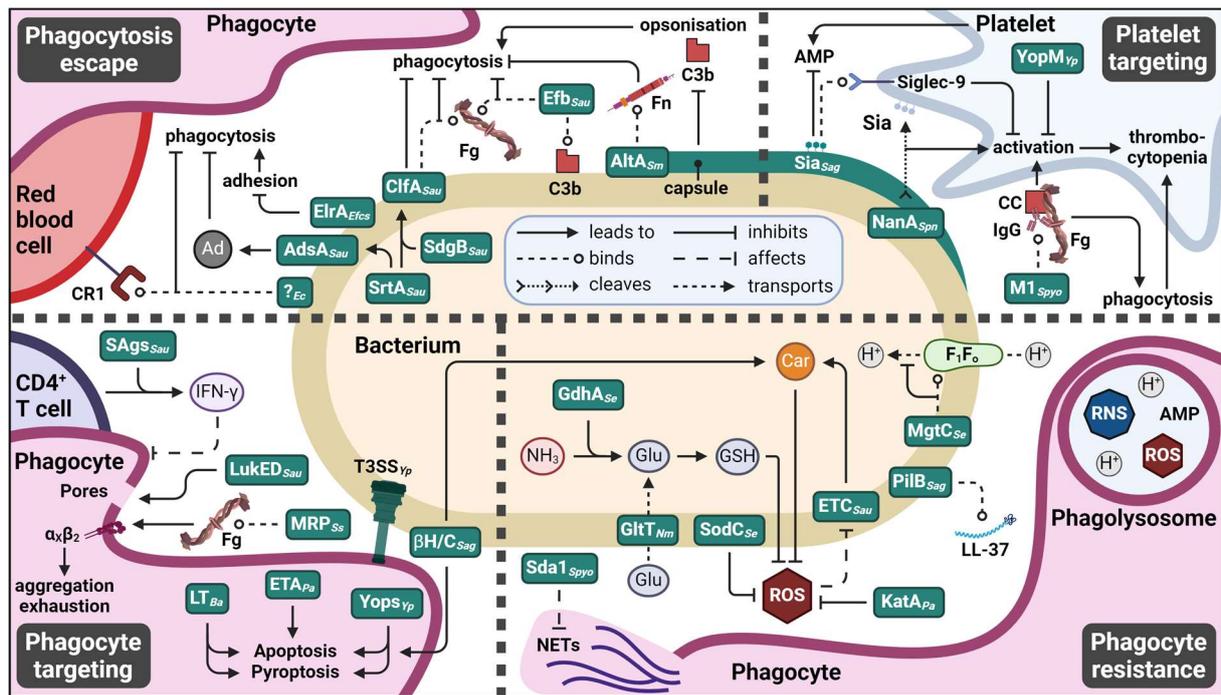


Figure 6.

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2419 **Figure 6.** Examples of bacterial factors (green) subverting host cell defenses in the
 2420 blood. Bacterial species: *Ba*: *Bacillus anthracis*. *Ec*: *Escherichia coli*. *Efcs*: *Enterococcus*
 2421 *faecalis*. *Nm*: *Neisseria meningitidis*. *Pa*: *Pseudomonas aeruginosa*. *Sag*: *Streptococcus*
 2422 *agalactiae*. *Sau*: *Staphylococcus aureus*. *Se*: *Salmonella enterica*. *Sm*: *Streptococcus*
 2423 *mutans*. *Spn*: *Streptococcus pneumoniae*. *Spyo*: *Streptococcus pyogenes*. *Ss*:
 2424 *Streptococcus suis*. *Yp*: *Yersinia pestis*. Abbreviations: Ad: adenosine. AMP: antimicrobial
 2425 peptide. Car: carotenoid. CC: complement components. CR1: complement receptor 1.
 2426 Fg: fibrinogen. Fn: fibronectin. Glu: glutamate. GSH: glutathione. IgG: immunoglobulin G.
 2427 NET: neutrophil extracellular trap. RNS: reactive nitrogen species. ROS: reactive oxygen
 2428 species. Sia: sialic acid. T3SS: type 3 secretion system.

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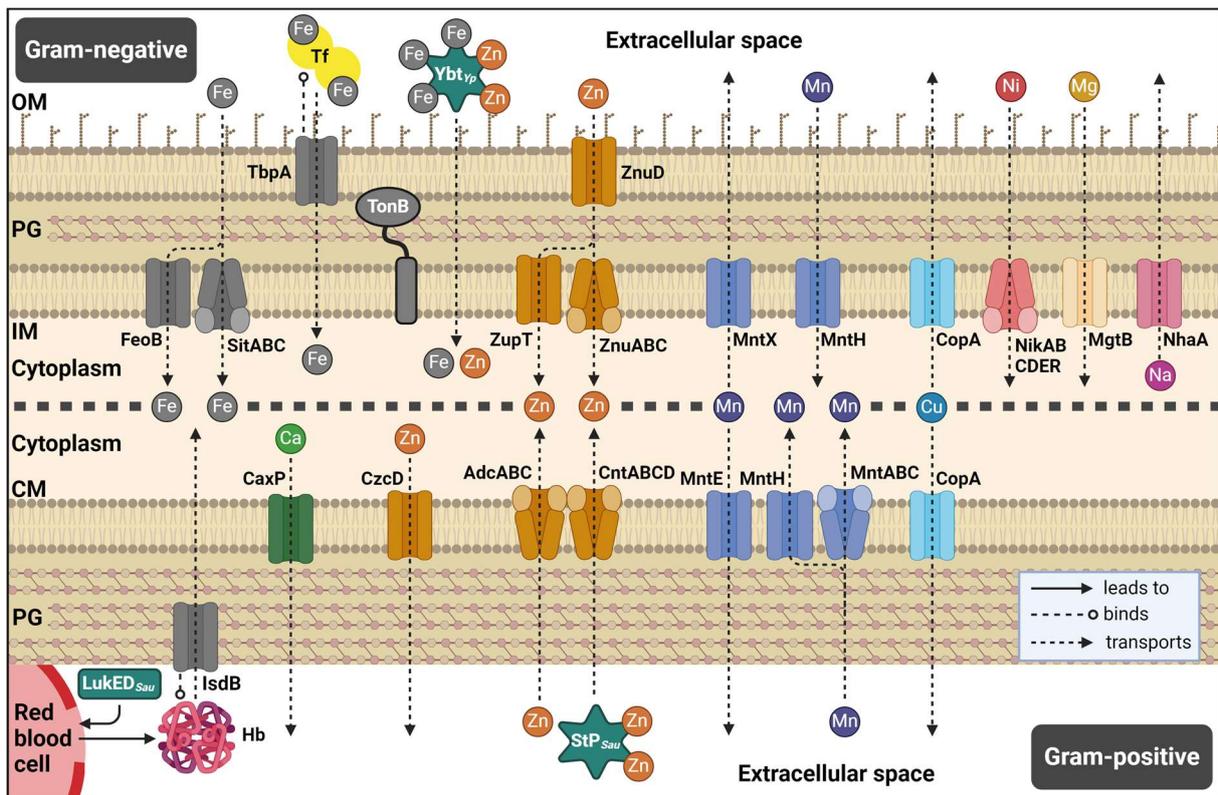


Figure 7.

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2432 **Figure 7.** Examples of bacterial factors subverting nutritional immunity in the blood.2433 Bacterial species: *Sau*: *Staphylococcus aureus*. *Yp*: *Yersinia pestis*. Metals: Ca: calcium.

2434 Cu: copper. Fe: iron. Mg: magnesium. Mn: manganese. Na: sodium. Ni: nickel. Zn: zinc.

2435 Abbreviations: CM: cytoplasmic membrane. Hb: hemoglobin. IM: inner membrane. OM:

2436 outer membrane. PG: peptidoglycan. Tf: transferrin.

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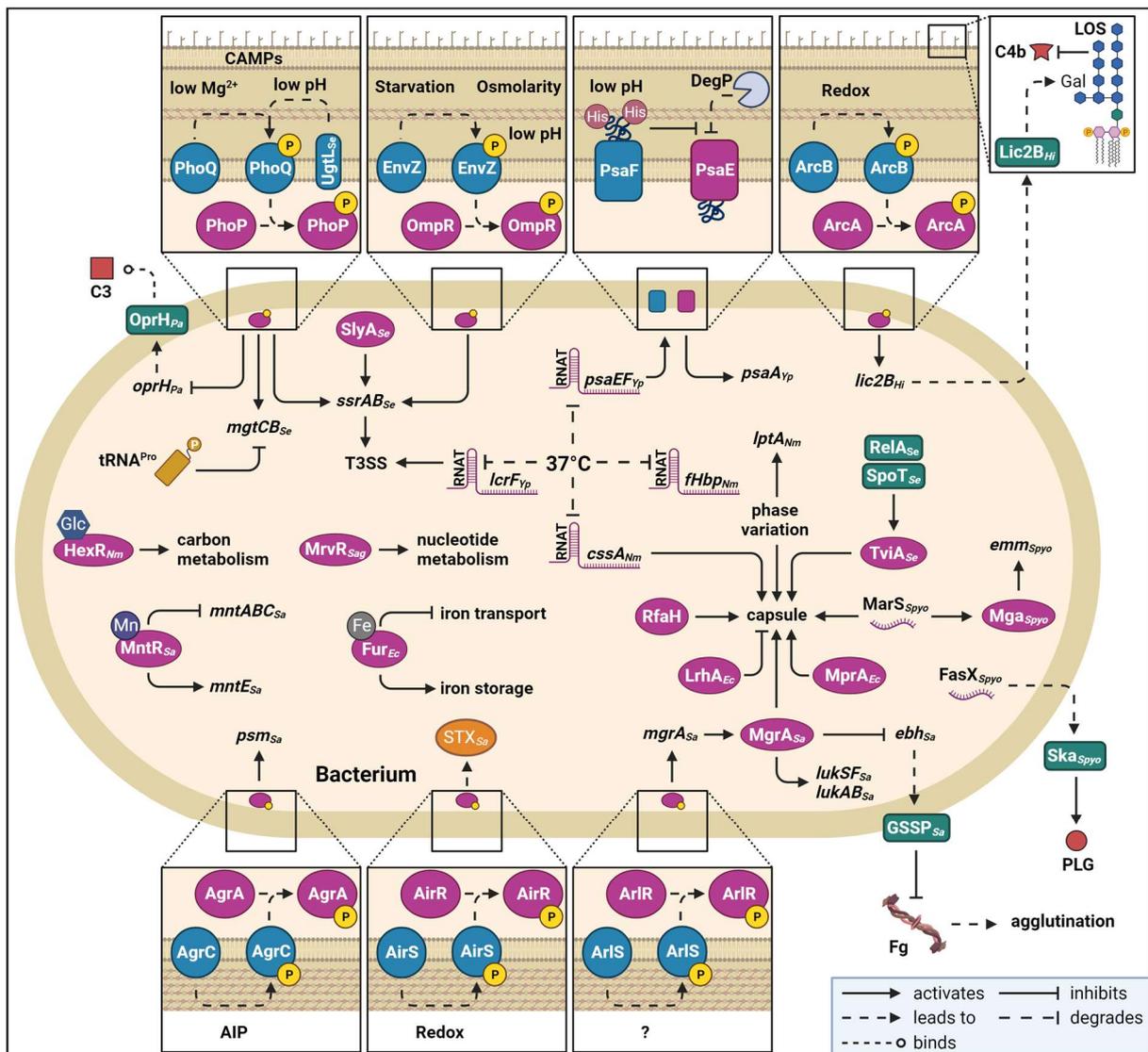


Figure 8.

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Figure 8. Examples of bacterial regulatory mechanisms involved in adaptation and survival in blood. Regulators are in purple, secondary factors helping in regulation are in blue and bacterial effectors are in green. Bacterial species: *Ec*: *Escherichia coli*. *Hi*: *Haemophilus influenzae*. *Nm*: *Neisseria meningitidis*. *Pa*: *Pseudomonas aeruginosa*. *Sag*: *Streptococcus agalactiae*. *Sau*: *Staphylococcus aureus*. *Se*: *Salmonella enterica*. *Spyo*: *Streptococcus pyogenes*. *Yp*: *Yersinia pestis*. Abbreviations: AIP: auto-inducing peptide. AMP: antimicrobial peptide. Fe: iron. Fg: fibrinogen. Glc: glucose. His: histidine. LOS: lipooligosaccharide. Mn: manganese. P: phosphate. PLG: plasminogen. RNAT: RNA thermometer. STX: staphyloxantin.

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2450 **Box 1. The complement system**

2451 The complement cascade can be activated by three different pathways upon bloodstream
2452 infection: the classical pathway (CP), the lectin pathway (LP) and the alternative pathway
2453 (AP). The three pathways lead to cleavage of C3 and C5 components and activation of the
2454 terminal pathway (TP) (Figure 1).

2455 The CP is activated by binding of the C1 complex, composed of the scaffold of C1q
2456 subunits and the C1s and C1r proteases, to immunoglobulins (Ig) bound to a bacterial antigen
2457 or alternatively by binding of C1 to the C-reactive protein (CRP), recognizing phosphocholine
2458 on bacterial surfaces. The LP is activated by mannose-binding lectin (MBL) and ficolins,
2459 complexed with mannose-binding lectin-associated proteases 1 and 2 (MASP-1 and MASP-
2460 2), and bound to specific target carbohydrates on bacterial surfaces (Figure 1.Ia). Both
2461 complexes recruit and cleave C4 then C2 components into C4a, C4b, C2a and C2b
2462 components, forming the C3 convertase C4b2b (formerly known as C4b2a). C4b2b cleaves
2463 C3 in C3a and C3b (Figure 1.IIa), when C4b is not degraded by the coordinated action of
2464 C4b-binding protein (C4BP) and the factor I protease (fI). The AP is first activated by
2465 deposition of C3b and factor B (fB) on bacterial surface. The deposited C3b is a product of
2466 the soluble C3 convertase, composed of C3 bound to H₂O and factor B (Figure 1.Ib), or of C3
2467 convertases from the other pathways, the AP also serving as an amplification loop. C3b
2468 bound to factor B and stabilized by properdin (factor P, fP) forms a C3 convertase, C3bBb (or
2469 C3bBbP) (Figure 1 IIb). Factor I can cleave C3b in inactive C3b (iC3b), an opsonin binding to
2470 complement receptor 3 (CR3). It was recently shown that MASP-3 is the activator of factor D
2471 (fD), linking the LP to the AP (Hayashi *et al.* 2019). FD in turn activates the AP by cleaving
2472 factor B, generating C3(H₂O)Bb and C3bBb. Factor H (fH) and factor I prevent activation of
2473 the AP.

2474 C3 convertases cleave C3 in C3a and C3b. C3a is a multifunctional peptide required for
2475 chemotaxis, which binds to C3a receptor (C3aR), and activates immune cells. C3b is an
2476 opsonin that binds to complement receptor 1 (CR1) and is essential for the propagation of

2477 the complement cascade. C3b binds to all C3 convertases, forming C5 convertases C4b2b3b
2478 (CP/LP) (Figure 1.IIIa) and C3bBb3b (AP) (Figure 1.IIIb), which cleave C5 in C5a and C5b.
2479 C5a is a chemoattractant for immune cells. Upon binding to the bacterial surface, C5b triggers
2480 the TP. C5b deposition recruits C6, C7, C8 and C9 that insert and polymerize in the bacterial
2481 membrane, forming the membrane-attack complex (MAC), a pore forming complex resulting
2482 in bacterial lysis (Figure 1.IV). MAC assembly can be negatively regulated by heparin-binding
2483 vitronectin, clusterin, CD59 or the cartilage oligomeric matrix protein (COMP). For
2484 comprehensive views of the structure, function and dynamics of the complement system, the
2485 reader is referred to previous reviews (Walport 2001; Ricklin *et al.* 2010; Schatz-Jakobsen *et*
2486 *al.* 2016; Mastellos *et al.*, 2023).

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2492 **Box 2. Transposon-based mutational screens**

2493 Transposon-based mutational screen approaches rely on mutant libraries generated by
2494 random transposition in the genome. These pooled libraries can then be used to screen
2495 mutants for various phenotypes such as resistance to serum or survival in blood, by
2496 measuring the differences in mutant abundance between the input and the output. Several
2497 techniques have been developed over the years:

- 2498 • **STM:** The first signature-tagged mutagenesis (STM) was developed in 1995. It
2499 consisted of unique nucleotidic tags inserted in the transposon. Depletion of specific
2500 mutants in a pool was revealed by hybridization arrays (Hensel *et al.* 1995).
- 2501 • **TraSH:** To circumvent the small size of pools in STM, another technique called
2502 transposon site hybridization (TraSH) was developed. It is based on genomic DNA
2503 hybridization on microarray (Sasseti *et al.* 2001).
- 2504 • **TIS:** Higher throughput is now achieved by next-generation sequencing (NGS), which
2505 opened new possibilities in transposon screening and led to the development of
2506 transposon insertion sequencing (TIS) falling into four different methods: transposon
2507 sequencing (**Tn-seq**), transposon-directed insertion sequencing (**TraDIS**), insertion
2508 sequencing (**INSeq**) and high-throughput insertion tracking by deep sequencing
2509 (**HITS**) (Cain *et al.* 2020).

2510 These screens have been widely used to discover new factors involved in bacteremia of
2511 the most clinically relevant bacteria such as *S. aureus* (Mei *et al.* 1997; Coulter *et al.* 1998;
2512 Benton *et al.* 2004; Christiansen *et al.* 2014; Valentino *et al.* 2014; Oogai *et al.* 2016; Groma
2513 *et al.* 2020) or *E. coli* (Phan *et al.* 2013; Subashchandrabose *et al.* 2013; McCarthy *et al.*
2514 2018; Ma *et al.* 2021) as well as other bacteria associated with bloodstream infection such as
2515 *A. baumannii* (Subashchandrabose *et al.* 2016; Sanchez-Larrayoz *et al.* 2017), *Citrobacter*
2516 *freundii* (Anderson *et al.* 2018), *E. faecium* (Zhang *et al.* 2017), *H. influenzae* (Langereis and
2517 Weiser 2014), *K. pneumoniae* (Short *et al.* 2020; Holmes *et al.* 2022), *Leptospira interrogans*
2518 (Lourdault *et al.* 2016), *N. meningitidis* (Sun *et al.* 2000; Geoffroy *et al.* 2003; Mendum *et al.*

2519 2011; Capel *et al.* 2017), *Pasteurella multocida* (Fuller *et al.* 2000), *Proteus mirabilis*
2520 (*Armbruster et al.* 2019), *P. aeruginosa* (Janet-Maitre *et al.* 2023), *S. enterica* (Hensel *et al.*
2521 1995; Chaudhuri *et al.* 2009), *S. marcescens* (Anderson *et al.* 2017), *S. agalactiae* (Hooven
2522 *et al.* 2018; Zhu *et al.* 2020; Dammann *et al.* 2021), *Streptococcus equi* (Charbonneau *et al.*
2523 2020), *S. pneumoniae* (Polissi *et al.* 1998; Mann *et al.* 2012), *S. pyogenes* (Le Breton *et al.*
2524 2013; van Hensbergen *et al.* 2018), *S. suis* (Arenas *et al.* 2020), *Y. pestis* (Palace *et al.* 2014)
2525 or *Y. pseudotuberculosis* (Crimmins *et al.* 2012). Additionally, a genetic screen using a library
2526 of *K. pneumoniae* transposon mutant recently identified factors required for bacterial survival
2527 in human serum (Weber *et al.* 2020). The mode of action of most of these factors remains to
2528 be deciphered.

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