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ORIGINAL ARTICLE

Chronic use of oral iron supplements is associated with poor clinical outcomes in patients with gram-negative bacteremia

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Abstract

An unabsorbed dietary iron supplementation can modify the colonic microbiota equilibrium and favor the growth of pathogenic strains over barrier strains. Nevertheless, the impact of oral iron supplements (OIS) use on the clinical outcomes of patients with gram-negative bacteremia (GNB) has not been evaluated. To explore the impact of OIS on the outcomes of patients with GNB. A retrospective study conducted in a tertiary hospital including patients with GNB during 2011–2016. The entire cohort was divided into chronic OIS users (study group) and nonusers (control group). The two groups were compared for the study outcomes, septic shock at presentation, length of hospital stay (LOS), and short-term mortality. The study cohort included 232 patients; 44 patients in the study group and 188 in the control one. There was no any significant difference in demographic and comorbidities characteristics between the two groups. *Escherichia coli* comprised the majority of bacteria (69%), while the urinary tract was the main source of the bacteremia. OIS alone and after adjustment was significantly associated with septic shock at presentation (OR = 2, CI95% [1.03–5], $p = 0.04$ and OR = 5, CI95% [1.4–15], $p = 0.01$, respectively). By multivariate analysis, OIS was significantly associated with 30-day mortality (OR = 3, CI95% [1.05–7], $p = 0.04$), but had no impact on LOS (16 + 23 vs. 12 + 15, $p = 0.9$). There is a significant association between chronic OIS exposure and increased adverse outcomes in patients with GNB. These findings might have important clinical implications.

Introduction

Iron deficiency is the most prevailing micro-nutritional deficiency among humans and the most common cause of anemia worldwide. Oral iron supplements (OIS) usually employ highly soluble forms of iron given in a large non-physiological bolus doses rendering iron more able to be absorbed [1, 2].

Iron is an essential nutrient for survival and replication of most microorganisms including fungi, protozoa, gram-positive and gram-negative bacteria [1]. For the enteric gram-negative bacteria (*Salmonella, Shigella, or* pathogenic *Escherichia coli*), iron acquisition plays an essential role in the virulence and colonization of most pathogenic strains. These bacteria vigorously compete for unabsorbed dietary iron in the colon by using receptors that bind transferrin, lactoferrin, and hemoglobin or by using low molecular mass siderophores that acquire iron either from the host proteins or from low molecular mass iron compounds [3–5].

An increase in unabsorbed dietary iron supplementation can modify the colonic microbiota equilibrium and favor the growth of pathogenic strains over barrier strains [6, 7]. A recent ex vivo growth characteristics evaluation of exemplar sentinel bacteria including *Escherichia coli, Yersinia enterocolitica, Salmonella enterica* serovar Typhimurium, and *Staphylococcus epidermidis* in adult sera, revealed markedly elevated growth in the serum collected after iron supplementation. Growth rates were strongly correlated with transferrin saturation ($p < 0.0001$ for all cases) [2].

Gram-negative bacteremia (GNB) is a frequent cause of sepsis in both hospitalized and community-dwelling patients, associated with high morbidity and mortality. The urinary tract is the

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most frequent source of GNB, while the gastrointestinal and biliary tracts are also sources of it [8, 9].

We speculate that patients with GNB who are chronically treated by OIS will have a more aggressive clinical course and worse prognosis attributed to the higher virulence of bacillary bacteria.

The aim of the study was to explore the impact of recent chronic use of OIS on the outcomes of hospitalized patients with GNB.

Methods

Subjects and study design

All consecutive hospitalized patients (> 18 years) with microbiologically confirmed GNB, that were hospitalized in one of the six medical wards of Beilinson hospital, Petah-Tikva, Israel, between 2011 and 2016, were eligible for the study. Patients younger than 18 years and ones with missing data were excluded.

The collected data, all from the medical records and based on previous diagnosis, included: demographics (age and gender), comorbidities (Charlson's score, diabetes mellitus, ischemic heart disease, congestive heart failure, previous stroke, chronic kidney disease, chronic obstructive pulmonary disease, dementia, active malignancy, solid organ transplantation, chronic steroid use), bacteremia origin (primary or secondary to urinary tract, gastrointestinal and biliary tracts or to central venous catheters), microbiological details (organism identification and antimicrobial susceptibility profile), appropriateness of empiric therapy (see definition), mechanical ventilation and use of vasopressors during hospitalization, septic shock at presentation, length of stay (LOS) as well as short-term mortality (in hospital and 30 days).

The eligible patients were divided into ones who were strictly used OIS at least 3 months prior to the index hospitalization (study group) and ones who were not (control group). The strictly use of OIS was verified by retrieving the pharmacy purchase reports. The two groups were compared for the study outcomes including, septic shock at presentation, LOS, in hospital, and 30-day mortality.

Definitions

Gram-negative bacteremia was defined as growth of one of the following Enterobacteriaceae species: *E.coli, Klebsiella pneumonia, and Proteous mirabilis* in one or more blood cultures.

Septic shock was defined as systolic blood pressure < 90 mmHg and more than one of the following systemic inflammatory response syndrome: fever > 38.3 °C or < 36 °C, WBCs > 12(k/ml^3) or < 4000 (k/ml^3), heart rate > 90 beat/min, respiratory rate > 20 breaths/min [10].

Appropriate empiric therapy was defined as antibiotics matching the in vitro susceptibility of the pathogen and given before culture results were available and within the first 48 h of the index point.

Resistant bacteremia: Bacteremia with resistant microorganism including extended spectrum beta lactamases (ESBL), ampC, and carbapenemase resistance enterobacteriaceae (CRE).

Microbiology methods

Bacterial isolates were detected from blood cultures using the BACTEC™ blood culture system /BACTEC™ FX system (Becton Dickinson, Inc., Sparks, MD, USA). Isolates identification was based on Vitek 2 system [11] or Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) [12]. Antimicrobial susceptibility was based either on Vitek 2 system or by the disc diffusion method.

Statistical analysis

We used the chi-square test for comparing dichotomous variables; continuous data was expressed as mean ± standard deviation or as median and interquartile range (25–75 percentiles) as appropriate and compared by using the *T* test. Clinically relevant variables that were associated with septic shock and mortality on univariate analysis were included into a logistic regression model. Two-sided *p* values, 0.05 were considered statistically significant.

Results

Study cohort

Two hundred thirty-two patients met the study inclusion criteria. Forty-four subjects strictly used iron supplements during the 3 months prior to index admission (the study group) and 188 did not (the control group). Their demographic and clinical characteristics are provided in Table 1.

There was no significant difference in demographic and comorbidity properties between the two groups. The urinary tract was the source of the bacteremia in approximately two thirds of the cases. *E.coli* was the major pathogen causing bacteremia (69%) followed by *Klebsiella pneumonia* (20%) and *proteous mirabilis* (11%). More than two third of the patients in each group had been treated by appropriate empiric antibiotic regimen. Resistance bacteremia rates were not significantly different between the study groups (25% vs. 24%, $p = 0.8$).

Septic shock

Of the entire cohort, 35 (15%) presented with septic shock. In univariate and multivariate analysis, septic shock was associated with OIS therapy during the last 3 months prior to admission (OR = 2, CI95% [1.03–5], $p = 0.04$) and OR = 5, CI95% (1.4–15), $p = 0.01$, respectively) (Table 2).

Table 1 Baseline characteristics of patients with gram-negative bacteremia who used iron supplementation and who did not

Characteristics	Iron exposure* ($n = 44$)	Non-iron exposure ($n = 188$)	p value
Demographics			
Age, mean ± SD (years)	80 ± 16	78 ± 15	0.6
Male gender (n, %)	18 (41%)	88 (47%)	0.5
Charlson score, mean ± SD	8 ± 2	7 ± 3	0.03
Body mass index(kg/m^2), mean ± SD	25 ± 5	26 ± 6	0.3
Comorbidites			
Diabetes mellitus (n, %)	23 (52%)	61 (32%)	0.02
Dementia (n, %)	8 (18%)	16 (9%)	0.09
Chronic obstructive pulmonary disease (n, %)	6 (14%)	12 (6%)	0.1
Congestive heart failure (n, %)	10 (23%)	27 (14%)	0.2
Chronic kidney disease (n, %)	5 (11%)	10 (5%)	0.2
Previous stroke (n, %)	7 (16%)	18 (10%)	0.3
Solid organ transplantation (n, %)	2 (5%)	16 (9%)	0.5
Chronic steroid use (n, %)	9 (20%)	29 (15%)	0.5
Ischemic heart disease (n, %)	13 (30%)	48 (26%)	0.6
Active malignancy (n, %)	10 (23%)	44 (23%)	1
Microbiologic features			
Primary bacteremia (n, %)	13 (30%)	48 (26%)	0.3
Urinary tract origin (n, %)	26 (59%)	109 (58%)	0.3
Gastrointestinal or biliary tracts origin (n, %)	2 (5%)	22 (12%)	0.3
Secondary to central line infection (n, %)	3 (7%)	4 (2%)	0.3
Resistant bacteremia** (n, %)	11 (25%)	45 (24%)	0.8
Appropriate empiric therapy*** (n, %)	28 (64%)	127 (68%)	0.4

*Iron exposure more than 3 months

**Resistant bacteremia: bacteremia with resistant microorganism including extended spectrum beta lactamases (ESBL), ampC, and carbapenemase resistance enterobacteriaceae (CRE)

***Appropriate empiric therapy: antibiotics matching the in vitro susceptibility of the pathogen and given before culture results were available and within the first 48 h of the index point

Length of hospital stay

The hospital stay of patients who were on OIS tended to be longer than the one of the control group (16 ± 23 vs. 12 ± 15, $p = 0.3$).

Mortality

The in-hospital mortality rate of the entire cohort was 22% (51/232). Univariate and multivariate analysis of risk factors for in-

Table 2 Multivariate model for factors associated with septic shock at presentation

Variable	Septic shock		OR (CI95%)	p value
	Yes ($n = 35$)	No ($n = 197$)		
Mechanical ventilation (n, %)	21 (60%)	12 (6%)	34 (11–5110)	< 0.0001
Iron exposure (n, %)	11 (31%)	33 (17%)	5 (1.4–15)	0.01
Male gender (n, %)	22 (63%)	84 (43%)	3 (1.1–9)	0.03
Congestive heart failure (n, %)	11 (31%)	26 (13%)	3 (0.9–8)	0.07
Age, mean ± SD	81 ± 13	78 ± 16	1.02 (0.9–1.1)	0.5
Resistance microorganisms (n, %)	13 (37%)	43 (22%)	1.4 (0.3–6)	0.7
Charlson score, mean ± SD	8 ± 3	7 ± 3	1 (0.8–1.3)	0.8
Appropriate empiric therapy (n, %)	21 (60%)	134 (68%)	0.6 (0.1–4)	0.8

Table 3 Univariate and multivariate analysis for factors associated with in-hospital mortality

Variable	In-hospital mortality		Unadjusted odd ratio (CI95%)	*p* value	Adjusted odd ratio (CI95%)	*p* value
	Dead (*n* = 51)	Survived (*n* = 181)				
Mechanical ventilation (*n*, %)	18 (35%)	15 (8%)	6 (3–13)	< 0.0001	7(2–21)	0.0005
Male gender (*n*, %)	34 (67%)	72 (40%)	3(1.5–5)	0.001	4(2–8)	0.002
Iron exposure (*n*, %)	12 (24%)	32 (18%)	1.5(0.6–3)	0.3	2 (0.9–5)	0.09
Age, mean ± SD	80 ± 15	78 ± 16	1 (0.9–1.03)	0.4	1(0.9–1.1)	0.3
Cardiovascular support* (*n*, %)	12 (24%)	10 (6%)	5 (2–13)	< 0.0001	2(0.4–7)	0.4
Appropriate empiric therapy (*n*, %)	35 (69%)	120 (66%)	1 (0.4–2)	0.9	2(0.5–8)	0.4
Resistance microorganisms (*n*, %)	11 (22%)	45 (25%)	0.9 (0.4–2)	0.7	0.9(0.3–4)	0.9
Charlson score, mean ± SD	8 ± 3	7 ± 2	1.2(1–1.3)	0.05	0.9(0.8–1.2)	0.9

SD standard deviation

*Cardiovascular support defined as the use of vasopressors

hospital mortality did not reveal a significant association between OIS therapy prior to hospitalization and in-hospital mortality (OR = 1.5 CI 95% [0.6–3], $p = 0.3$ and OR = 2, CI95% [0.9–5], $p = 0.09$, respectively) (Table 3).

The 30-day mortality rate of the entire cohort was 20% (46/232). In univariate analysis, OIS was not associated with 30-day mortality (OR = 1.7 [0.8–4], $p = 0.2$). But after adjustment to age, gender, charlson score, parameters of severity (mechanical ventilation and the use of vassopressors), the appropriateness of empiric antibiotic therapy and resistant bacteremia, the model revealed a significant association between OIS therapy prior to hospitalization and 30-day mortality (OR = 3, CI95% [1.05–7], $p = 0.04$) (Table 4).

Discussion

The study results reveal that chronic OIS use 3 months prior to hospitalization with GNB is independently associated with septic shock at presentation and 30-day mortality.

There is an ongoing discussion whether an excess of serum iron increases the risk of infections and their severity. Regarding malaria, there was a debate whether an excess of iron load increases the risk of malaria in children living in endemic areas. However, a recent Cochrane systematic review found that iron does not cause an excess of clinical malaria (RR = 0.93, 95%CI [0.87–1.00] [13]. Nevertheless, in vitro and in vivo studies involving humans and animals concluded that excess of iron has been found to impair neutrophil and T cell function (acute immunosuppressive state) and to promote microbial growth [14–16]. Impairments in neutrophil migration, phagocytosis, and survival had been observed in healthy volunteers' neutrophils that were incubated with ferric compounds [17–19]. Failure to mount a Th1-mediated protective immune response to *Candida albicans* infection has been observed in mice that were overloaded with iron dextran. Interestingly, treatment with iron chelator restored the Th1 response and the ability to survive the infection [20].

In an ex vivo study evaluating the growth characteristics of exemplar sentinel bacteria including *Escherichia coli,*

Table 4 Univariate and multivariate analysis for factors associated with 30-day mortality

Variable	30-day mortality		Unadjusted odd ratio (CI95%)	*p* value	Adjusted odd ratio (CI95%)	*p* value
	Dead (*n* = 46)	Survived (*n* = 186)				
Mechanical ventilation (*n*, %)	15 (33%)	18 (10%)	4.5(2–10)	0.0002	4 (1.4–14)	0.009
Male gender (*n*, %)	30 (65%)	76 (41%)	2.6(1.3–5)	0.004	3 (1.3–7)	0.008
Iron exposure (*n*, %)	12 (26%)	32 (17%)	1.7(0.8–4)	0.2	3 (1.1–7)	0.04
Age, mean ± SD	82 ± 14	78 ± 16	1 (0.9–1.05)	0.2	1.04 (0.9–1.1)	0.07
Cardiovascular support (*n*, %)	11 (24%)	11 (6%)	5(2–12)	0.0006	3(0.7–10)	0.2
Resistance microorganisms (*n*, %)	9 (20%)	47 (25%)	0.7 (0.3–2)	0.5	0.5 (0.1–2)	0.4
Charlson score, mean ± SD	8 ± 3	7 ± 3	1.1(1–1.3)	0.04	0.9 (0.8–1.2)	0.7
Appropriate empiric therapy (*n*, %)	30 (65%)	125 (67%)	0.8 (0.3–2)	0.7	0.8 (0.2–4)	0.8

Yersinia enterocolitica, Salmonella enterica serovar Typhimurium, and *Staphylococcus epidermidis* in adult sera revealed a markedly elevated growth in the serum collected after iron supplementation. Growth rates were strongly correlated with transferrin saturation ($p < 0.0001$ for all cases) [2].

Our study results suggest that iron exposure has a negative impact on the clinical course and prognosis of GNB which is speculated to be attributed to the elevated growth of hypervirulent gram-negative bacteria after iron exposure. Although there was no any difference in the rates of resistance bacteremia among the OIS users and nonusers, further microbiological laboratory based studies are needed to explore this theory.

This study has important clinical and preventive implications on the management of patients with GNB. We assume that prompt stopping of OIS therapy once GNB is suspected might affect the clinical outcomes. In addition, a more strict prescription strategy of OISs in "high risk" patients for GNB, like the ones with indwelling urinary catheters or central venous lines with previous blood stream infections, should be seriously considered.

The study has several limitations: First, its retrospective nature makes it vulnerable to collection bias and to potential inaccuracy in data collection. Second, it is a single-center study, limiting the generalizability of the results. Third, the small sample size might decrease the significance of the results; a larger multicenter database will increase the significance of the results and the study's external validity.

In conclusion, this study showed a significant association between recent chronic oral iron exposure and increased clinical adverse outcomes in hospitalized patients with GNB. These findings might have important clinical implications for preventing GNB and when it is identified.

SD standard deviation

SD standard deviation

SD standard deviation

Author contributions Study concept and design: Elis A, Bishara J, and Atamna A contributed to study conception and design and analyzed the data

Acquisition, analysis, or interpretation of data: all authors

Drafting the manuscript: Atamna A and Hamud H draft the manuscript

Critical revision of the manuscript for important intellectual content: all authors

Compliance with ethical standards

Ethical approval The study was approved by the hospital's Ethics Committee.

Informed consent Not applicable.

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References

1. Miller JL (2013) Iron deficiency anemia: a common and curable disease. Cold Spring Harb Perspect Med 3(7)
2. Cross JH (2015) Oral iron acutely elevates bacterial growth in human serum. Sci Rep 5:16670
3. Weinberg ED (2009) Iron availability and infection. Biochim Biophys Acta 1790(7):600–605
4. Andrews SC (2003) Bacterial iron homeostasis. FEMS Microbiol Rev 27(2–3):215–237
5. Bezkorovainy A, Kot E, Miller-Catchpole R, Halofis G, Furmanov S (1996) Iron metabolism in bifidobacteria. Int Dairy J 6:905–919
6. Naikare H, Palyada K (2006) Major role for FeoB in Campylobacter jejuni ferrous iron acquisition, gut colonization, and intracellular survival. Infect Immun 74(10):5433–5444
7. Zimmermann MB, Chassard C (2010) The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. Am J Clin Nutr 92(6):1406–1415
8. Suárez CJ, Lolans K, Villegas MV, Quinn JP (2005) Mechanisms of resistance to beta-lactams in some common gram-negative bacteria causing nosocomial infections. Expert Rev Anti-Infect Ther 3(6): 915–922
9. Sligl W, Taylor G, Brindley PG (2006) Five years of nosocomial gram-negative bacteremia in a general intensive care unit: epidemiology, antimicrobial susceptibility patterns, and outcomes. Int J Infect Dis 10(4):320–325
10. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international Sepsis definitions conference. Crit Care Med 31(4):1250–1256
11. Meurman O, Koskensalo A, Rantakokko-Jalava K (2006) Evaluation of Vitek 2 for identification of yeasts in the clinical laboratory. Clin Microbiol Infect 12(6):591–593
12. Dhiman N, Hall L, Wohlfiel SL, Buckwalter SP, Wengenack NL (2011) Performance and cost analysis of matrix-assisted laser desorption ionization-time of flight mass spectrometry for routine identification of yeast. J Clin Microbiol 49(4):1614–1616
13. Neuberger A, Okebe J, Yahav D, Paul M (2016) Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev 27(2):CD006589
14. Ishida JH, Johansen KL (2014) Iron and infection in hemodialysis patients. Semin Dial 27(1):26–36
15. Parkkinen J, von Bonsdorff L, Peltonen S, Gronhagen-Riska C, Rosenlof K (2000) Catalytically active iron and bacterial growth in serum ofhaemodialysis patients after i.v. iron-saccharate administration. Nephrol Dial Transplant 15(11):1827–1834
16. Deicher R, Ziai F, Cohen G, Mullner M, Horl WH (2003) High-dose parenteral iron sucrose depresses neutrophil intracellular killing capacity. Kidney Int 64(2):728–736
17. Sengoelge G, Kletzmayr J, Ferrara I, Perschl A, Horl WH, SunderPlassmann G (2003) Impairment of transendothelial leukocyte migration by iron complexes. J Am Soc Nephrol 14(10):2639–2644
18. Ichii H, Masuda Y, Hassanzadeh T, Saffarian M, Gollapudi S, Vaziri ND (2012) Iron sucrose impairs phagocytic function and promotes apoptosis in polymorphonuclear leukocytes. Am J Nephrol 36(1): 50–57
19. Van Asbeck BS, Marx JJ, Struyvenberg A, van Kats JH, Verhoef J (1984) Effect of iron (III) in the presence of various ligands on the phagocytic and metabolic activity of human polymorphonuclear leukocytes. J Immunol 132(2):851–856
20. Mencacci A, Cenci E, Boelaert JR, Bucci P, Mosci P, Fe d'Ostiani C et al (1997) Iron overload alters innate and T helper cell responses to Candida albicans in mice. J Infect Dis 175(6):1467–1476