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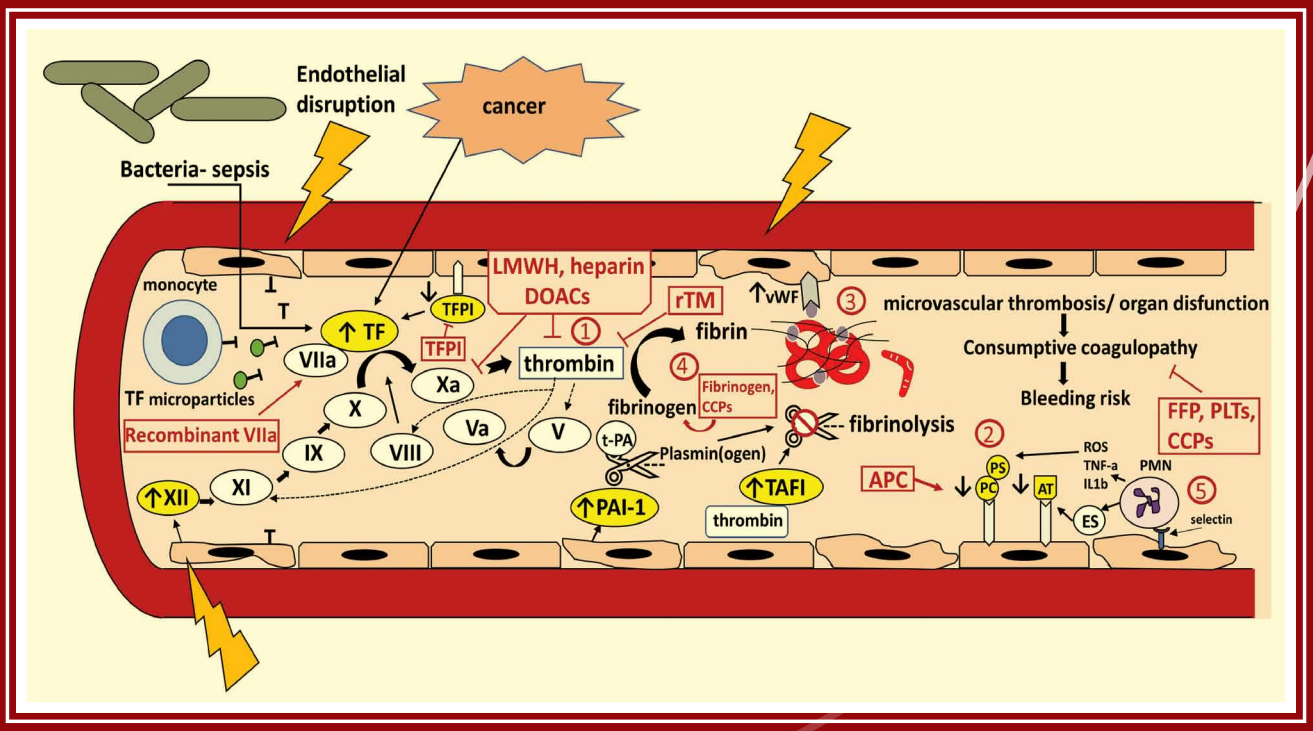

Disseminated intravascular coagulation pathophysiology

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Akinosoglou et al. discusses the current landscape of fungal infections and the development of resistance and outlines the novel treatment regimens for the management of these infections. The editorial by Binou et al. deals with a novel hypolipidemic therapy, namely bempedoic acid, and its probable use as monotherapy or adjunctive therapy on the current standard. Lastly, the editorial by Athanasopoulos et al. presents the main aspects of nocturnal polyuria, discussing its pathophysiology, diagnosis, and treatment management.

Moreover, this issue includes three review articles. The review article by Bianco et al. evaluates the epidemiology and etiology of focal nodular hyperplasia, explores the clinical presentation and diagnostic challenges including differential diagnoses, and characterizes the radiological and histopathological features of said lesions. Moreover, this editorial assesses the management and surveillance strategies of focal nodular hyperplasia. The review by Verigou et al. provides data on the pathogenesis of disseminated intravascular coagulation (DIC) and describes the etiology, epidemiology, pathophysiology, diagnostic procedures, clinical manifestations and the supportive measures recommended as treatment strategies for the patients with DIC.

Lastly, the review by Sotiropoulos et al. outlines the up-to-date strategies for the initial management of acute non-variceal upper gastrointestinal bleeding, its causes, timing of endoscopy, patient's risk stratification and the role of proton pump inhibitors and antithrombotic agents in this setting.

Yours sincerely,

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New antifungals: Where do we stand?

Karolina Akinosoglou, Despina Papageorgiou, Charalambos Gogos

The landscape of fungal infections has progressively changed over the years with the emergence of antifungal resistance constituting a growing problem in clinical practice and compromising successful patient outcomes [1]. While significant progress has been achieved in the development of novel agents, the survival rates for certain fungal infections have not improved. Some fungal species remain neglected and lack effective therapeutic options and multiple drug related limitations persist.

Resistance occurs due to selective pressure from the increased usage of antifungal drugs in empiric therapy and involves a number of mechanisms depending on their action, such as gene mutations, drug target modification, efflux pumps etc. [1]. Yet another reason for the emergence of resistance is antifungal prophylaxis. Although prophylactic therapy is proven to effectively prevent invasive fungal infections and improve survival of high-risk populations [patients with hematologic malignancies and allogeneic hematopoietic stem cell transplantation (HSCT)], some of these patients may develop breakthrough infections. When such infections occur, they often involve difficult to treat drug resistant pathogens [2].

Antifungal drug resistance is not the sole concern when dealing with fungal infection treatment. There are other drug associated factors that complicate treatment and emphasize the need for improvement of existing medications. Currently, mostly utilized agents have an oral route of administration with multiple limitations, cause significant adverse effects and induce drug-drug interactions. Also, toxicity and unstable pharmacokinetic parameters that impact drug efficacy, necessitate mention.

And even though there are currently plenty of therapeutic options available for *Candida* infections, the management of other rising difficult to treat molds and yeasts such as *Mucorales, Fusarium, Lomenospora*, and *Scedosporium*, is far more complex. Of note, despite our advances, survival rates of *Aspergillus* infection have not risen beyond 70% through the last 20 years [3-5]. This underscores the presence of numerous unmet needs in the treatment of fungal infections. To address this barrier, multiple strategies are currently under investigation. Hopefully, the development of novel antifungal drugs in addition to repurposing or establishing new methods of delivery of existing agents will enhance the available treatment options and achieve more favorable patient outcomes.

To this end, a number of new agents in currently used classes are currently coming out of the clinical research pipeline. Otesoconazole is a novel oral agent that differs from other azoles because it contains a tetrazole moiety instead of triazole or imidazole. This modification produces better selectivity for fungal CYP51 with less interaction with off-target human CYPs and improves the safety profile [6]. Otesoconazole is FDA approved for the treatment of recurrent vulvovaginal candidiasis (VVC) and demonstrated efficacy for onychomycosis treatment compared to itraconazole [7].

Opelconazole is a novel inhaled triazole with a broad spectrum against yeasts and molds. The inhaled route of administration achieves high local concentrations in the lung, rendering it a promising agent for invasive aspergillosis treatment including COVID-19 associated pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis. The topical use maximizes local activity while minimizing systemic toxicity and drug-drug interactions [1].

Rezafungin is a next generation echinocandin, derived from anidulafungin. It has echinocandin-expected in-vitro activity against *Candida* spp and has a chemical

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modification that confers high stability, a longer half-life, and allows for a once-a-week dosing regimen [8]. A completed trial (ReSTORE) examined the rezafungin 400-mg/200-mg once-weekly regimen for the treatment of candidemia and invasive candidiasis. The active comparator was intravenous caspofungin. Rezafungin was non-inferior to caspofungin for the primary endpoints of day-14 global cure and 30-day all-cause mortality. Compared with other echinocandins in phase 3, results showed improved efficacy and safety. An ongoing trial (ReSPECT) is designed to evaluate the drug's role as prophylaxis [9].

Ibrexafungerp is a novel triterpenoid antifungal that shares mechanism of action with echinocandins. After two successful trials, VANISH 303 and 306, the FDA approved ibrexafungerp for the treatment of vulvovaginal candidiasis [10]. Another ongoing study (FURI) evaluates the role of ibrexafungerp as treatment for patients who are either intolerant of standard antifungal therapy or have not responded to standard therapy. The study has already shown that oral ibrexafungerp provides a favorable therapeutic response in patients with challenging fungal disease and limited treatment options [11].

Another approach in the battle against fungal infections is the development of new methods of delivery for established agents. Alternative AmB formulations are currently under investigation and contain cochleates, nanoparticles and umbrellas. The intended objective is to target delivery, minimize toxicity and improve efficacy. Among the aforementioned, an oral encochleated form of AmB (MAT2203) is the furthest along clinical development [7]. There is a completed study for VVC that resulted in lower cure rates and more adverse effects in comparison to fluconazole. Phase 1 and phase 2 studies on cryptococcal meningitis in HIV infected patients are ongoing [7]. Oral cAmB was well tolerated when given in 4-6 divided daily doses without the toxicities commonly seen with IV AmB [12].

Last, we have been happy to see new agents with a totally new mechanism of action arising from clinical trials**.** Olorofim is the first member of a novel antifungal class, orotomides. The mechanism of action was identified during genetic screening of *Aspergillus nidulans* and is based on inhibition of dihydroorotate dehydrogenase (DHODH), a key enzyme for pyrimidine biosynthesis. The agent has *in vitro* activity against difficult-to-treat *Aspergillus* spp. with intrinsic and acquired antifungal resistance [13]. It is active against *Lomentospora, Scedosporium, Coccidioides* and *Fusarium* spp but lacks activity against mucorales and yeasts [1]. Interim results of a phase-2b, open-label trial (study 32) suggest that olorofim, when compared to relevant historical controls or expected outcomes for highly active, uncontrolled invasive fungal infection, has a positive benefit-risk profile in a well-defined population of patients with limited or no treatment options [14].

Fosmanogepix is a prodrug of the antifungal manogepix which targets glycosylphosphatidylinositol-anchored protein maturation through inhibition of the fungal enzyme Gwt1. This impacts fungal cell integrity, growth, and virulence [1]. The drug showed potent activities against most *Candida* species., except for *Candida krusei*. Compared to fluconazole, itraconazole, voriconazole, amphotericin B, and micafungin, fosmanogepix showed equally potent activities against fluconazole-resistant and fluconazole-susceptible *Candida* strains. It also had potent activities against various filamentous fungi, including *Aspergillus fumigatus* and it was active against *Fusarium solani* and some black molds. Given its broad spectrum of activity, fosmanogepix is likely to be a promising agent for the treatment of invasive fungal infections [15].

Last repurposing other drugs as antifungals remained always an option. Sertraline, a commonly prescribed antidepressant, offers a promising treatment option for cryptococcosis, notably for cryptococcal meningitis. Sertraline's ability to accumulate in central nervous system is a valuable characteristic relatively to other antifungal drugs. Contrasted with fluconazole, sertraline showed narrower range of inhibitory concentrations against multiple cryptococcal isolates which translates into a lower probability of resistance occurrence. In addition, a synergistic fungicidal effect with fluconazole was observed in a mammalian model and could potentially mark the shortening of treatment duration and the reduction in resistance emergence [16]. The role of Tamoxifen derivatives and related agents have also been investigated for similar purposes. The research pointed out the structural requirements for antifungal activity of these agents [17]. Calcineurin inhibitors also serve as repositionable candidates. There is evidence that calcineurine is required for virulence based on research on many human fungal pathogens including *C. albicans* and *C. neoformans*. Calcineurin fulfills critical functions in fungal growth, transition between morphological states and stress response. Thus, fungal specific calcineurin inhibitors, which do not cross react with human calcineurin causing im-

munosuppression must be developed, so as to be used as combination therapy for fungal infections [18]. Lastly, ebselen and auranofin exhibit potential for drug repurposing. Both agents demonstrated antifungal and anti-biofilm activities and presented synergistic effects when combined with other antifungal agents, thus rendering them promising candidates for combination therapy [19, 20].

In conclusion, there has been an extraordinary surge in the development of novel antifungals, including meaningfully different formulations, distinct new agents in existing antifungal classes and drugs with completely novel mechanisms of action and potential for spectrum targeting in difficult to treat fungi. However, whether these drugs are to address all our unmet needs is to be seen, since difficult to treat infections including *Mucorales* remain neglected. But most importantly, within our departments of critical care and immunocompromised patients, we need to be able to determine early enough those at high risk of specific infections, so as to provide meaningful prophylaxis or therapy in order to ensure successful outcomes. Unfortunately, at the moment, our diagnostic armamentarium remains limited in terms of sensitivity and specificity hampering therapeutic efforts, and underlining the need for parallel development of both diagnostic and therapeutic tools.

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Bempedoic acid: An equally efficacious alternative to statins?

Petroula Binou[1], Christos Katsioulis[2], Emmanouil Sinakos[1]

Bempedoic acid [1] is a substance that was recently approved for the treatment of dyslipidemia (familial or not) in patients in need of pharmacological treatment, where the optimal statin therapy is contraindicated or not tolerated or as adjuvant treatment to conventional antilipidemic therapy in patients where target low-density lipoprotein cholesterol (LDL-C) is not achieved. It is mostly excreted via renal route (up to ~30% in stool). Bempedoic acid, not currently marketed in Greece, is a prodrug which after activation in its sulfate ester formation from the coenzyme A inhibits the ATP citrate lyase (ACL). ATP citrate lyase is a major participant in cellular metabolism, mainly due to the fact that it is the primary source of acetyl-Coenzyme A, which by itself is a precursor for cholesterol and fatty acid synthesis, as well as, protein acetylation. It is apparent then, that APT citrate lyase inhibition agents are a probable effective way in reducing lipid-related pathologies.

The need for hypolipidemic therapy in patients with evidenced cardiovascular disease, for secondary prevention, is well established, as well as the need for primary prevention in individuals at high risk with comorbidities, either due to metabolic syndrome or familial hypercholesterolemia. In 2019, the European Society of Cardiology presented, during their annual symposium, the new guidelines for the treatment of dyslipidemia, as well as the goals for different patient groups, mainly aiming for a >50% decrease in the LDL-C baseline setting a <55 mg/dl target for the very high risk group, a <70 mg/dl for the high risk group, a <100 mg/dl for the intermediate risk group and a <116 mg/dl LDL-C target for the low risk group, respectively. Dietary adjustments, weight loss and smoking cessation, irrespective of pharmacotherapy, remain the cornerstone of the dyslipidemia treatment.

The use of statin or rather Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors for the treatment of dyslipidemia dates back to the 80's, with lovastatin being the first statin approved for marketing in 1987. A well-established necessity for an effective lipid-lowering drug in order to alleviate the cardiovascular risk burden was previously poorly fulfilled, while the available treatments (cholestyramine, fibrates, mainly clofibrate and nicotine acid), as well as the usual dietary adjustments, were far from potent. During the 90's various statins were synthesized (pravastatin being the first followed by simvastatin, atorvastatin, fluvastatin, pitavastatin and rosuvastatin) presenting different strengths in various dosages. In the 00's, ezetimibe, another lipid-lower agent, was added to the standard pharmacotherapy as adjuvant treatment in patients not achieving their LDL-C goals or as monotherapy in patients not able to receive statin therapy. As with the vast majority of drugs, statins are not shy of side effects, with the most common being liver/pancreatic enzymes elevation, myopathy and rhabdomyolysis and neuropathy, while drug-drug interaction is mostly presented in cyclosporin, protease inhibitor, gemfibrozil and warfarin coadministration. A diabetes mellitus predisposition is also noted in statin use, mainly rosuvastatin.

A novel drug group, the PCSK9 inhibitors (PCSK9i) [2], was approved for the treatment of dyslipidemia

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in 2015 following research beginning in 2003. PCSK9 inhibitors are part of the monoclonal antibodies drug group effectively targeting the PCSK9 enzyme and reducing the LDL-C serum levels. The primary indication for PCSK9 inhibitors, in their advent, was the secondary prevention in patients presenting with familial hypercholesterolemia not adequately controlled on conventional therapy or in patients who could not tolerate statins and were poorly controlled while on ezetimibe. As of 2021, PCSK9i received indication for primary prevention in patients with homozygous familial hypercholesterolemia not achieving their LDL-C goals while on conventional therapy.

As of 2020, bempedoic acid [3] was added in the pharmacotherapy arsenal against dyslipidemia [4]. In April 2023, the CLEAR Outcomes, a drug vs placebo double-blind study, was published, in which bempedoic was compared to placebo comparing efficacy in MACE (Major Adverse Cardiovascular Events). CLEAR Harmony was another study that was concluded in 2019, in which patients with known atherosclerosis and/or heterozygous familial hypercholesterolemia [5], who received the maximally tolerated statins, were provided with bempedoic acid and were compared to patients that received placebo concerning MACE, again during the 52-week trial bempedoic did not lead to a higher incidence of adverse effects and led to significantly lower LDL-C levels. The result in CLEAR Outcomes was the predominance of bempedoic vs placebo suggesting that bempedoic is a safe alternative to statin treatment or primary option in patients unable to receive them.

In international literature, even before CLEAR Outcomes [6] was published, bempedoic was used on patients presenting with homozygous familial hypercholesterolemia that were unable to treat with or could not tolerate statins, who were already on PCSK9i and did not achieve their LDL-C goal. Consequently, subsequent published studies [7] examined the concomitant use of bempedoic acid, ezetimibe, and the maximal tolerated statin dose vs a control group and confirmed the superiority of the triple-therapy group on the grounds of effectiveness of lipid-lowering strategy and cardiovascular risk control.

A recent study [8] indicates the efficacy of standard dose bempedoic regimen administration, in LDL-C reduction, up to 30%, while the addition of ezetimibe would result in a 45% decrease. Adjunctive administration of bempedoic to high intensity statin therapy, however, did not present an adequate reduction in LDL-C, maintaining a 15% lowering effect compared to statin monotherapy, while a near 30% reduction was observed in the combination of PCSK9i-bempedoic. An increased risk of new-onset diabetes is well established, reaching approximately 12%, when statin therapy is prescribed as lipid-lowering therapy, possibly by affecting the pancreatic beta-cell function by promoting insulin resistance and having a deleterious effect on GLP-1 (glucagon-like peptide 1) [9]. Bempedoic presented no such interference concerning glucose metabolism and insulin resistance, which was observed in most studies, thus making it a preferable therapeutic regimen to statins, when indicated.

During the period between 2020 and 2022 a series of studies were published [10,11], examining the safety profile and bempedoic pharmacodynamics, the first of them being CLEAR Wisdom [12]. All of them coalesced in assuring that bempedoic acid is a safe, alternative, option for statin therapy. Bempedoic acid, as aforementioned, is a prodrug that inhibits ACL by intervening in the ketogenesis pathway having as a final result the increase of LDL receptors and the clearance of low-density lipoproteins in the serum. The prodrug activation is mostly induced in the intracellular environment, chiefly in liver cells and in lesser extent in renal cells, whereas no activity is observed in adipose or muscle tissue, the latter possibly being the reason of miniscule risk of rhabdomyolysis.

In conclusion, bempedoic constitutes a safe and efficacious choice [13] of hypolipidemic drug therapy that could be prescribed as adjunctive medication to the standard of care or as monotherapy [14], even as an alternative to PCSK9i possibly on the basis of potential reduced cost, in patients either not achieving the LDL-C target values under maximal tolerated statin therapy and/or ezetimibe, or presenting inability to receive statin therapy [15]. It should also be noted that bempedoic would be a possible alternative to primary initiation of statin therapy in patients at high risk of developing new-onset diabetes, due to its neutral effect on pancreatic beta-cells, and further investigation of the role of bempedoic ought to be made, concerning its possible effect in liver steatosis and non-alcoholic fatty disease.

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Sinakos E.: conceived the idea and reviewed the manuscript for important intellectual content.

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What is the significance of Nocturnal polyuria in Nocturia?

Anastasios Athanasopoulos

Nocturia is a significantly underestimated medical problem that seriously affects patients' quality of life, work engagement, productivity, and well-being. It is a common condition, proven to be the most bothersome for patients with Lower Urinary Tract Symptoms [1]. It is well known that two or more nocturnal voids are the clinically meaningful threshold associated with significant adverse consequences to health and well-being [2]. Commonly associated consequences include increased mortality and morbidity, increased risk of falls and hip fractures, traffic and work accidents, increased risk of cardiovascular diseases, and diabetes mellitus [2]. Additionally, interrupted sleep patterns can contribute to mood disturbances, such as irritability and depression [2]. It also provokes immunological problems and dysfunction of memory and perception, daytime fatigue, decreased productivity and work performance, and impaired cognitive function. Overall deteriorates the quality of life and increases health costs [2,3].

Hence, the importance of taking sleep into account should be emphasized when assessing the relationship between nocturia and associated outcomes [3]. It is worth mentioning that nocturia is just as prevalent in women as in men, especially in postmenopausal women [4,5].

Regarding pathophysiology, the main causes that provoke nocturia are nocturnal polyuria, global polyuria, urinary bladder dysfunction, sleep disorders, and circadian clock disorders. Urinary bladder dysfunction includes reduced bladder capacity, detrusor overactivity, and other mixed etiologies [6].

Nocturnal polyuria is a medical condition characterized by excessive urine production during the night, leading to disrupted sleep patterns and frequent nighttime bathroom visits. Despite its prevalence, this condition is frequently undiagnosed or overlooked, resulting in considerable discomfort and a diminished overall quality of life for affected individuals. Two definitions of nocturnal polyuria exist. The classical and widely adopted definition considers nocturnal polyuria as nocturnal urine production above 20% for young patients and 33% for older patients (>65y) [2]. The other definition defines nocturnal polyuria as nocturnal urine production of >90 ml/h during night sleep [5].

Nocturnal polyuria is more common than one might think, particularly among the elderly. However, due to its often-subtle symptoms and limited awareness, many cases go undiagnosed or misdiagnosed as other conditions, such as overactive bladder or urinary tract infections. Nocturnal polyuria seems to be the most common cause of nocturia. According to the prevailing definition [7], the prevalence of nocturnal polyuria, in both genders, is 44% in those under 65 years, and 31.3% in those 65 years or older [8]. In a recent study, 31.5% of men and 38,5 of women had nocturnal polyuria when the classical definition was used and 23.8% and 18.1% of men and women respectively presented nocturnal polyuria under the nocturnal urine production definition [9]. It seems that more research and evidence are needed to reach a consensus about the most accurate definition for use in everyday clinical practice [10].

Numerous factors can contribute to the development of nocturnal polyuria. Several non-urological causes are known to provoke this dysfunction. Such causes are untreated diabetes mellitus or insipidus,

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sleep disorders because of obstructive sleep apnea, cardiovascular diseases (hypertension, heart failure) [11], chronic kidney disease, certain medications, varicose veins of the lower extremities, and primary polydipsia. Identifying and addressing these risk factors appropriately is pivotal in effectively managing and treating nocturnal polyuria. If there is not any obvious disorder provoking nocturnal polyuria, the condition is classified as nocturnal polyuria syndrome [12,13]. The interplay among nocturnal polyuria and pathological conditions such as hypertension, arteriopathy and arterial stiffness, coronary heart disease, and distribution in the third space of body fluid is deemed significant and the focus of current research [13]. This is also observed in the context of the role of brain natriuretic peptide [13].

Nocturnal polyuria leading to nocturia, with a constant need to wake up and urinate that disrupts sleep and yields consequential outcomes. The coexistence of nocturia resulting from urological conditions, such as overactive bladder and bladder outlet obstruction and nocturnal polyuria aggravates the whole clinical condition.

The diagnosis of nocturnal polyuria involves a thorough assessment of an individual's medical history, physical examination, and specialized tests, such as urine volume measurement and frequency charts. Notably, in the case of nocturnal polyuria, a frequency-volume chart serves as the cornerstone for the diagnosis of this condition [14].

Following diagnosis, diverse treatment options are available, including lifestyle modifications, behavioral therapies, and pharmacotherapy. It is essential for healthcare professionals to be knowledgeable about these options and work closely with patients to develop personalized treatment plans [6].

The treatment rationale for nocturia underscores that nocturnal polyuria, attributed to inadequate antidiuresis, is a major contributing factor to nocturia. Before starting any pharmaceutical treatment, it would be beneficial to try some lifestyle modifications, as these can offer an improvement of nocturnal polyuria. For instance, reducing caffeine, alcohol, and generally fluid intake a couple of hours before bedtime, could be of benefit to the patient [14]. Furthermore, the administration of desmopressin offers a significant reduction in nocturia episodes and nocturnal urine production, leading to improvements in sleep and quality of life [15-18]. Contemporary formulations of desmopressin are well-tolerated, with a relatively low risk of hyponatremia with appropriate dosing escalation. A lower minimum effective dose in females is needed compared to males [18-20]. Furthermore, sodium monitoring just before treatment initiation and on the first, third, and seventh days of treatment is essential. Research for the treatment of nocturnal polyuria is ongoing and includes highly selective arginine vasopressin 2 receptor agonists, non-steroid anti-inflammatory drugs, sex hormone replacement treatment, and short-acting diuretics [18].

Raising awareness about nocturnal polyuria is crucial to ensure timely diagnosis and effective management. Individuals grappling with frequent nighttime urination should refrain from dismissing it as a routine aspect of aging or underestimating its impact on their well-being. Initiating a dialogue with healthcare providers, and openly discussing symptoms, can pave the way for early intervention and subsequently enhance overall quality of life.

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Focal Nodular hyperplasia

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Abstract

Hepatic Focal Nodular Hyperplasia (FNH) is a benign lesion characterized by the proliferation of hepatocytes and non-parenchymal cells. The etiology remains unclear. However, the higher female preponderance and the fact that FNH may grow in size during pregnancy may suggest a hormonal influence. These tumors are typically discovered incidentally on ultrasonography, computed tomography or magnetic resonance imaging. These imaging modalities reveal the characteristic "spoke-wheel" pattern of arterial enhancement, which is highly suggestive of FNH. Confirmation via histological examination may be necessary in cases of diagnostic uncertainty. In most instances, FNH is a benign and self-limited condition that does not necessitate treatment. However, surgical resection may be considered if the lesion is symptomatic or enlarging. Liver-sparing surgical techniques are preferred to preserve hepatic function. In conclusion, FNH is a benign hepatic lesion predominantly affecting women of childbearing age. Its characteristic radiological features and generally indolent course make it distinguishable from malignant liver lesions. Clinicians should consider conservative management and close monitoring in most cases, reserving surgical intervention for specific indications.

Key words: *Focal Nodular Hyperplasia; imaging; liver*

INTRODUCTION

Asymptomatic benign liver lesions are being increasingly identified on abdominal imaging. First described in 1958 by pathologist Hugh Edmonson M.D., focal nodular hyperplasia (FNH) is the second most common of such solid benign lesions, only surpassed by hemangiomas. Table 1 demonstrates the most commonly encountered benign liver lesions [1].

OBJECTIVES

The aims of this short literature review were to assess the epidemiology and etiology of FNH, explore the clinical presentation and diagnostic challenges including differential diagnoses, and characterize radiological and histopathological features of said lesions. Efforts were also made to evaluate its management and surveillance strategies.

METHODOLOGY

This literature review was conducted through two databases: PubMed and Google Scholar. The primary keywords used included "Focal Nodular Hyperplasia", "FNH", "Hemangioma" and "Benign Liver tumors". Boolean operators ("AND", "OR") were used. Only articles published in English and involving humans were used. Articles pertaining to epidemiology, etiology, clinical presentation, radio-histopathological features, and management were retrieved. Only articles published from the year 2000 onwards were included in this literature review.

EPIDEMIOLOGY

FNH is found in 0.3-3% of the adult population, most commonly in the 30-40 age group [1]. In contrast, it is found in 0.02% of the pediatric population [2]. Developing factors might shed light as to why there is a dif-

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Table 1. *Solid Benign liver lesions [1].*

Liver Lesion	Incidence in the adult population (%)
Hemangiomas	3-20%
Focal nodular hyperplasia	0.3-3%
Hepatic Lipoma	1%
Hepatocellular adenomas	0.007-0.0012%
Biliary Duct Hamartoma	0.6 – 5.6%
Nodular regenerative hyperplasia	0.72%-2.6%

ference in FNH incidence between adults and children. A pediatric liver is still developing and hence might be less susceptible to hormonal or vascular changes which are key in the pathogenesis of FNH. These lesions tend to be asymptomatic, and children usually undergo less transabdominal imaging than adults, thus leading to underdiagnosis [3].

In both adults and pediatric patients, there is a female preponderance, with a female to male ratio of 9:1 being reached in adults [1].

Although FNH is most commonly found as one lesion, around 20-30% of cases involve multiple lesions (usually up to 5). The latter can occur in patients with vascular liver disorders such as hereditary hemorrhagic telangiectasia and Budd Chiari syndrome [4]. It is very rare for FNH to present with more than 5 separate lesions in the same individual [5]. In the pediatric setting, it has been reported in long term malignancy survivors raising the suspicion that bone marrow transplant and chemotherapeutic agents (including high dose alkylating agents) increase the risk of FNH development in this population [6].

The size of FNH can vary. The vast majority are less than 5 cm and near the liver surface. Cases of FNH larger than 10cm have been reported and these are usually resected [7].

ETIOLOGY

The exact etiology and pathogenesis of FNH are not yet fully understood. A characteristic feature of FNH when compared to other benign liver lesions is its origin. It arises from polyclonal cells resulting in a number of modifications including angiopoietin vascular remodeling [8,9].

FNH is therefore thought to occur following a hyperplastic reaction in the liver in response to a vascular malformation. Change in the oxygenation of liver parenchyma is the initial focus of FNH. Continued ischemia leads to the proliferation of bile ducts [10]. Both increase and decrease in blood flow have been found to have the potential to cause a hyperplastic reaction in the liver [8]. In fact, an increased incidence of FNH in conditions with vascular malformations has been reported such as in patients with hereditary hemorrhagic telangiectasia and hemangiomas [11,12]. Up to 20% of FNH lesions can be associated with hemangiomas [9].

While the exact etiology remains elusive, several studies have identified certain molecular patterns for FNH. Of these, increased expression of extracellular matrix genes leading to activation of transforming growth factor beta (TGF-b) is prominent [13]. Increased production of glutamine synthase through overexpression of the Wnt/ B-catenin target gene is also observed [14]. The latter leads to map-like pattern expression of glutamine synthase at the edges of the lesion, a feature unique to FNH [14].

FNH has also been described in response to blunt abdominal trauma and exposure to certain chemotherapeutic agents, particularly alkylating agents, and drugs such as azathioprine [15]. Smoking seems to increase the risk of FNH. A diet high in vegetables and whole grains may decrease the risk of FNH [16]. In animal models, a high-cholesterol diet has been associated with an increased risk of FNH. The relationship between these diets and FNH could be explained by an increase in TGF-B1 protein expression [17].

RELATIONSHIP WITH PREGNANCY AND ORAL CONTRACEPTIVE USE

There is a controversy about the relationship between FNH and hormones. The increased incidence in females suggests a correlation with estrogen. Moreover, females on oral contraceptives tend to have larger nodules than their male counterparts and females not on oral contraceptive medications [8].

Several cases have been described showing a reduction in FNH size following the withdrawal of the oral contraceptive pill (OCP). Other cases highlight size progression in pregnancy and regression following delivery [4]. Nevertheless, the European Association for the Study of the Liver (EASL) guidelines states that studies have not yet established the role of pregnancy and OCP in the development of FNH [9]. Furthermore, FNH runs a benign course in pregnancy [4] (Figure 1). Vaginal delivery is not associated with an increased risk

of complications [18]. The American College of Gastroenterology (ACG) guidelines make similar statements and advise that pregnancy and the use of OCP are not contraindicated in patients with FNH [19]. Female patients who have FNH and wish to continue OCP should be monitored every 2-3 years [19].

HISTOPATHOLOGY

Microscopically, one of the distinctive features is a central scar which is made up of collagen, arteries, and veins. Fibrous septae might be present which will form a pseudocapsule. These characteristics allow the histopathologist to differentiate FNH from other similar lesions including hepatocellular carcinoma, hepatocellular adenoma (HCA), and fibrolamellar hepatocellular carcinoma. FNH might also contain Kupfer cells and bile ducts [8].

Other histopathological characteristics have been described. The most prevalent of these include the absence of the classical central scar. This usually occurs in lesions that are less than 3cm in size. Another atypical finding is FNH with steatosis. Immunohistochemistry staining is commonly used in the assessment of FNH. Glutamine synthase expression in a map-like pattern at the peripheries of the nodule is unique to FNH [9]. The latter can be used in instances when imaging is unable to differentiate FNH from HCA [19].

DIAGNOSIS

Diagnosis is usually based on imaging. Histological diagnosis can be obtained in doubtful cases. Although ultrasound (US) may be the first imaging modality used to assess liver nodules, magnetic resonance imaging (MRI) is considered the best modality when it comes to diagnosing FNH. It has a specificity of almost 100% and a sensitivity of around 75%. The latter decreases in small FNH (<3cm). In this case, especially if the lesion is <3cm in size, a combination of contrast-enhanced ultrasound (CEUS) and MRI is usually performed [4]. The addition of hepatobiliary contrast media – such as gadobenate dimeglumine- can increase the sensitivity of MRI to 99% [8].

RADIOLOGICAL FEATURES

Focal nodular hyperplastic lesions have typical findings on US, computed tomography, and magnetic resonance imaging. This lesion is considered to be homogenous in most imaging modalities, except for the central scar. US assessment usually depicts a hypo or isoechoic lesion. CEUS depicts the characteristic "spoke on wheel" sign on the arterial phase in which centrifugal arteries radiate from a central artery [20]. CT scans show a homogeneous hyperdense lesion in the arterial phase which becomes hypo or isodense in the portal phase. T1-weighted images on MRI depict the lesion as iso or hypointense. Central scar is enhanced in the delayed phase using gadolinium. T2-weight images produce a hyper or isointense lesion [19]. FNH shows mild diffusion restriction on diffusion-weighted MRI. The central scar is best appreciated on MRI [4]. Table 2 summarizes the FNH radiological characteristics of the different radiological tests.

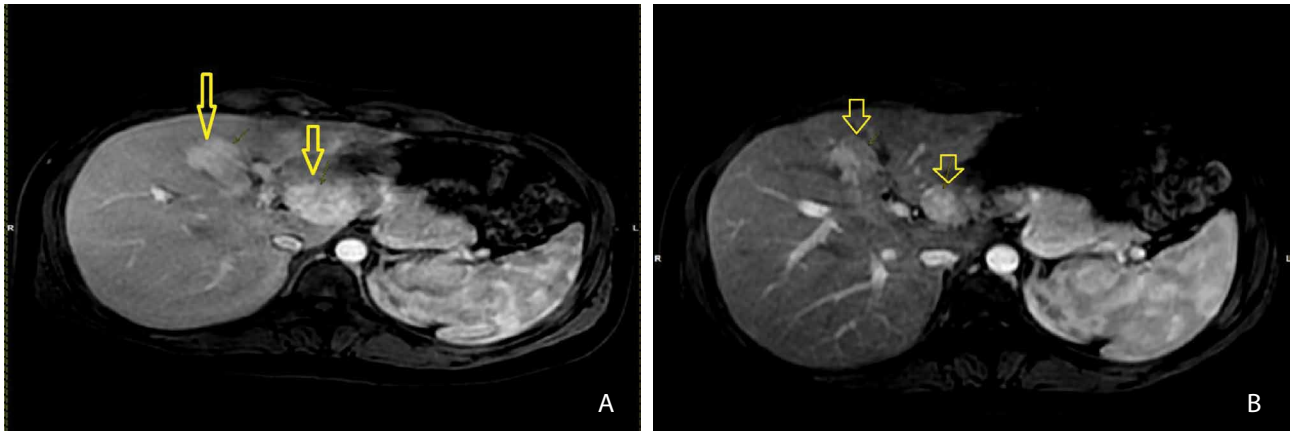

Figure 1. A and B: MR Liver/ Spleen arterial phase of a 28-year-old lady attending visits a Mater Dei Hospital, Malta. The patient was pregnant during the first MR Liver / Spleen (Figure 1A). The MR Liver/ Spleen was repeated in the following year (Figure 1B). Yellow arrows depict the presence of FNH in segments I and IV. One can easily appreciate the decrease in size of FNH from April 2021 (1A) to June 2022 (1B). Pregnancy was uneventful and no FNH-related complications occurred.

Table 2. *Radiological characteristics of FNH [7,19,28,29].*

Modality	Radiological Features
US	• Variable echogenicitiy • Doppler depicts increased vascularity in a centrifugal manner from a central vessel
CE-US	• Early arterial phase – Early enhancement with early centrifugal filling • Late arterial phase – Centrifugal filling • Portal venous phase – Enhancement – Scar may be visible (unenhanced)
CT	• Non-contrast – Hypo or isoattenuation – May appear hyperattenuating in cases of NASH • Arterial phase – Enhancement except central scar • Portal venous phase – Hyper or isoattenuation in contrast to the surrounding liver – Central scar retains hypoattenuation
MRI	• T1 – Iso or hypointense – Central scar is hypointense • T2 – Iso or hyperintense – Central scar is hyperintense • Gadolinium – Arterial phase: early enhancement – Portal venous phase: iso-hyperintense – Central scar retains contrast in delayed phases • Primovist – Arterial phase: early enhancement – Delayed arterial phase: enhances – Hepatobiliary phase: iso-tense, centra scar does not enhance
Tc-99m	• Sulfur colloid – Normal or increase uptake • HIDA – Increased uptake and delayed clearance

US: ultrasound; CE-US: Contrast enhanced ultrasonography; CT: Computed tomography; MR: Magnetic Resonance Imaging; Tc-99m: Technetium-99m; HIDA: hepatobiliary iminodiacetic acid

RADIOLOGICAL FNH MIMICKERS

Differential diagnosis of FNH includes other benign liver lesions as well as malignant ones. A feature similar to the "central scar" can be seen in fibrolamellar hepatocellular carcinoma, intrahepatic cholangiocarcinoma and HCA. It is important to differentiate FNH from the latter as HCA`s are associated with hemorrhage and malignant transformation [10]. US assessment of HCA depicts a heterogenous lesion which can be anechoic if bleeding or hyperechoic if steatotic. Cross-sectional imaging usually demonstrates a well demarcated lesion with peripheral enhancement [19].

Hemangiomas on the other hand are seen as hyperechoic nodules on ultrasonography and appear to have discontinuous peripheral enhancement with centripetal fill-in on cross-sectional imaging.

CLINICAL COURSE AND COMPLICATIONS

FNH is usually diagnosed incidentally through imaging, and most are therefore asymptomatic. Non-specific abdominal symptoms including early satiety and dyspepsia have been described. Abdominal pain may occur in large lesions due to compression of the liver capsule or pressure on surrounding organs [10]. An abdominal mass might be palpated in very large lesions. Biochemistry usually shows normal or mild derangement in liver enzymes, albeit this might be attributed to other underlying conditions. Of note, alpha-fetoprotein levels are normal [8].

The clinical course of FNH is usually benign. Malignancy has never been reported [21]. However, FNH has been reported to occur in association with other malignancies including hepatocellular carcinomas [22]. In FNH located near the liver surface, a rare complication that can occur is spontaneous intraperitoneal hemorrhage and rupture. This has been described in 10 cases so far (Table 3) [23]. The vast majority were women [23]. Fatal rupture and hemorrhage occurred in one patient in late pregnancy [24]. The preferred treatment option in this setting has been surgery [22,25].

MANAGEMENT

Both the European and American guidelines suggest a conservative approach to the management of FNH [9,19]. There is a poor correlation between FNH and symptoms; thus, conservative management is preferred even in the presence of non-specific symptoms. Active management in the form of surgical resection is only performed in specific cases such as in enlarging (usually a diameter of >7cm) and exophytic lesions. Another indication for resection is symptomatic FNH (as discussed above). The most common surgical option is usually hepatic resection. Both open and laparoscopic resection

Table 3. *Cases involving rupture of FNH [23].*

Patient Number	Year of publication	Age	Sex	Number of lesions	Maximal diameter (CM)	Management
1	1974	26	F	1	10	Surgery
2	1995	28	F	2	4.5	Surgery
3	2001	37	F	1	5	Pre-op TAE, Surgery
4	2003	27	F	1	6	Surgery
5	2005	35	F	1	9.8	Surgery
6	2005	42	F	1	10	Surgery
7	2006	37	F	4	5.2	Surgery
8	2006	26	F	N/M	15	Pre-op TAE, Surgery
9	2013	23	F	1	1	Diagnosis at Autopsy
10	2016	35	M	1	8	Pre-op TAE, Surgery

F: Female; M: Male; N/M: Not mentioned; CM: Centimetres; TAE: Trans-aterial chemoembolization

have been described [26]. Locoregional therapy in the form of embolization and radiofrequency ablation has been used in some patients, especially in those not fit for more invasive surgery [5,19].

SURVEILLANCE

Surveillance is generally not recommended. However, there is a difference in the recommendations of European and American guidance. According to European guidelines, once a diagnosis of FNH is made, there is no need for follow-up even in pregnancy and in patients on OCP. Furthermore, stopping oral contraceptive medications is not recommended [4]. Nonetheless, the American guidelines suggest annual ultrasonography assessment for 2-3 years after diagnosis is made in women who would like to continue oral contraceptive medication. Patients diagnosed with FNH and who are not on OCP do not require regular follow-up [19].

In patients diagnosed with FNH and who become pregnant, European guidelines do not recommend imaging surveillance [18]. At present, there is no guidance on females who are on hormone replacement therapy (HRT) and have concomitant FNH. It has been noted that hepatic hemangiomas which are commonly associated with FNH do increase in size and can rupture in women on oestrogen-based HRT [27].

CONCLUSION

FNH is a benign liver lesion frequently discovered incidentally. Its diagnosis can precipitate patient anxiety. Accurate diagnosis and appropriate management are crucial to avoid unnecessary interventions. Further research is warranted to enhance our understanding of FNH and improve its diagnosis and management.

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Disseminated intravascular coagulation: An uncontrolled explosion of coagulation leading to consumptive coagulopathy

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Abstract

Disseminated intravascular coagulation (DIC) is the result of an uncontrollable activation of the coagulation cascade that can affect patients of all ages with different underlying diseases and conditions and increases their mortality. Sepsis, cancer, major trauma, and obstetric emergencies are four of the main underlying conditions associated with DIC, followed by vascular malformations, hematological malignancies and entrance of foreign material in the vasculature. Patients exhibit different clinical manifestations from latent DIC (asymptomatic or indolent) to overt DIC with life threatening thrombotic or bleeding complications. The treatment of DIC requires complete understanding of the pathogenetic mechanisms, identification of the underlying causative disease, thorough physical examination and constant laboratory follow up; to evaluate the thrombotic versus bleeding risk of the patient and the severity of their clinical status, and choice of the appropriate supportive measures. The cornerstone of treatment for DIC remains the elimination of the underlying causative factor.

Key words: *Disseminated intravascular coagulation; DIC; coagulopathy; thrombosis; sepsis; cancer; hemostasis; intravascular hemolysis; hemolytic microangiopathy*

INTRODUCTION

Under normal conditions there are several and complex regulatory mechanisms, securing the preservation of the homeostatic balance between factors with prothrombotic, anti-thrombotic and fibrinolytic properties in the peripheral blood circulation in humans [1]. Following variable causality, a loss of this homeostasis may occur, ultimately leading to an uncontrolled activation of the coagulation cascade at different parts of the vasculature, a condition termed disseminated intravascular coagulation (DIC) [2]. The clinical manifestations of DIC vary greatly and range from absence of any clinical symptom and sign or the appearance of some minor cutaneous ecchymoses to severe symptoms and signs from the central nervous system (CNS), including coma and death [2]. Prognosis relies mainly on the underlying etiology and the prompt and effective management of the emerging condition. Several studies have elucidated various components of the pathogenesis of DIC, providing a solid basis for the application of several and different interventions for the restoration of coagulation and hemostasis pathways [3]. In this review, we aim to summarize long established as well as newer insights in the pathogenesis of DIC and describe the etiology, epidemiology, pathophysiology, diagnostic procedures, clinical manifestations and the supportive measures recommended as treatment options for the patient who suffers from DIC.

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EPIDEMIOLOGY

DIC may occur in about 30-50% of patients with sepsis [4] and it is developed at an estimated rate of about 1% among all hospitalized patients [5]. DIC occurs at all ages and in all races, and no particular sex predisposition has been noted. However, many chronic or latent cases may be underdiagnosed or misdiagnosed as manifestations of the underlying condition.

PATHOGENESIS OF DIC

DIC pathogenesis is multifactorial and not yet fully understood. Several deregulated mechanisms and pathways have been described during the past decades, indicating that there are at least five dominant pathogenetic events: 1. Excessive thrombin generation, 2. Immune-mediated (inflammation-mediated) thrombosis, 3. Inappropriate or excessive platelet activation, 4. Deficiency of natural anticoagulants and 5. Defective fibrin degradation [6].

Thrombin generation

Excessive thrombin generation is driven by the increased levels of circulating tissue factor (TF). TF is expressed by activated monocytes, endothelial or neoplastic cells and microparticles (MPs) of monocytes or monocyte -platelet complexes, depending on the underlying disease or condition which generates DIC and plays a crucial role in the activation and perturbation of the coagulation cascade [7,8]. Additionally, MPs from platelets and erythrocytes initiate thrombin generation independently of TF in a FXII-dependent manner [9].

The sum of these pathways results in a repetitive cycle of upregulation of thrombin production through platelet activation and consequently, the translocation of P selectin and the expression of TF, resulting in increased thrombin generation [10].

Immune-mediated (inflammation- mediated) thrombosis

TF expression is upregulated by immune signaling. Pattern recognition receptors (PRRs) binding pathogen-associated molecular patterns (PAMPs) [11], and/or host-derived DAMPs [12], or activating immunoglobulin Fc receptors are initiative signals for the generation of monocyte TF in infection [13]. Autoactivation of FXII can take place after contact with bacteria-derived long-chain polyphosphates (LC-poly-Ps) and platelet-derived short-chain polyphosphates (SC-poly-P) which initiates coagulation.

Protease-activated receptors (PARs) [14], complement mediators [15,16], P-selectin–mediated leukocyte interactions [17], and recognition of DAMPs [18] contribute to the immune mediated amplification of intravascular TF expression.

Proinflammatory cytokines [19], such as tumor necrosis factor (TNF), interleukin (IL)1-β, and IL-6, all have a procoagulant effect [20], and are overexpressed in DIC. Preclinical experimental sepsis models have highlighted the prothrombotic effect of proinflammatory cytokines through multiple pathways such as the downregulation of anticoagulant mechanisms [21], the support of endotheliopathies [22], and fibrinolysis modulation [23]. Even though promising, the use of TNF and IL-1 inhibitors in sepsis trials did not affect the incidence of DIC [24,25]. Other components of intravascular coagulation activation (thrombin activity, fibrin deposition and platelet aggregation) include the release of neutrophil extracellular traps (NETs; DNA coated in anti-microbial proteins) into the vasculature which results in microvascular hypoperfusion and end organ damage [26], as well as excessive complement activation. Complement and coagulation pathways interact in various ways. Anaphylatoxins, opsonins, and intermediates of the terminal complement complex are complement mediators with known procoagulant effects such as the inflammatory activation of vascular cells through C3a and C5a anaphylatoxins, or the alteration of endothelial permeability through PARs by C4. C5a induces TF expression by the endothelium, monocytes and neutrophils, and complement can also directly activate platelets, thus co-stimulating the cascade leading to thrombi formation in more than one manner [27].

Platelet activation

Endothelial damage, invading pathogens and sepsis -through either direct contact or circulating proinflammatory molecules- call for an immediate platelet response. Early thrombin generation activates platelets which through the release of pro-inflammatory, procoagulant and vasoactive molecules (prostaglandins, serotonin, adrenaline, PF4) and MPs as well as the exposure of procoagulant membrane phospholipids, aggravate the deregulation of coagulation pathways. Platelets express P-selectin, which further contributes to the inflammatory and procoagulant state in DIC, leading to the formation of microvascular thrombi and ultimately to the decrease of platelet count due to excessive consumption [28].

Deficiency of natural anticoagulants

The etiology of the deficiency of natural anticoagulants (antithrombin and proteins C/S deficiencies) in DIC is multifactorial. The increased consumption of the lately activated coagulation factors, particularly thrombin and fibrinogen, due to the continuous and abnormal activation of the coagulation pathway, the deficient hepatic production, the escape of molecules out of the intravascular space, the proteolytic inactivation of serum antithrombic proteins (mediated through the activity of elastase released by activated neutrophils) as well as the hemodilution occurring when multiple red blood cell transfusion therapy is required, are the main causes. Deficient replenishment of the consumed coagulation factors, resulting from inadequate production by the liver is not uncommon, and is attributed to primary or secondary liver failure, usually accompanying many of the primary causes of DIC. On the contrary, increased TF pathway inhibitor (TFPI) levels have been detected in sepsis-associated DIC, but the inhibitor's capacity to prevent thrombin generation initiated by TF in the systemic circulation is impaired [29,30,31].

Defective fibrin degradation/ fibrinolysis

Tissue plasminogen activator (t-PA) is a normal anticoagulant, released from endothelial cells upon the generation of traces of fibrin polymers in the circulation and initially activates plasminogen, leading to generation of plasmin, which enzymatically cleaves fibrin polymers and results to the formation of elevated levels of fibrin degradation products and particularly of D-dimers. This defensive process is rapidly reversed, due to the inhibition of t-PA by plasminogen activator inhibitor-1 (PAI-1), which is synthesized in the liver, regulated by immune modulators, and is expressed primarily by endothelial cells but is also released by thrombin-activated platelets. High plasma levels of circulating PAI have been associated with poor prognosis and high mortality in patients with DIC [32]. Another contributing factor to the inhibition of fibrinolysis is the activation of thrombin activatable fibrinolysis inhibitor (TAFI). TAFI activation is thrombomodulin dependent and its exact role in DIC is not fully understood [33,34]. In rare cases fibrinolysis is accelerated leading to a hyperfibrinolytic state and major bleeding manifestations, as seen in DIC related to acute promyelocytic leukemia (APL) [35].

ETIOLOGY

DIC is not a primary disease, but (it is) always a syndrome or a complication, secondary to another underlying disease or condition that induces the inappropriate activation of coagulation.

It is estimated that about 35% of all cases of severe sepsis may be complicated by DIC [36]. Classically, infection by Gram-negative bacteria has mainly been associated with DIC. However, according to published data the incidence of DIC in patients infected by Gram-positive cocci is similar [37]. Systemic infections or infestations caused by other microorganisms, including Neisseriae, fungi or parasites may lead to DIC, as well [37]. For example, high degree of parasitemia, primarily by *Falciparum* malaria, may be complicated by DIC and has been associated by high mortality rate [38].

DIC may emerge in the course of all types of neoplastic disorders, including hematological malignancies as well as solid tumors. In these diseases the coagulation cascade is activated as a result of the membrane surface expression of procoagulant factors by tumor cells. The incidence of DIC in cancer is not precisely known and may depend on the diagnostic criteria used. In some published series, particularly in patients with metastatic adenocarcinoma or in those with lymphoproliferative diseases, the reported incidence rises up to 20% in consecutive cases [39]. In these patients the risk of thrombosis is clearly greater than that of bleeding, but in severe cases, thromboembolism can be seen in conjunction with bleeding manifestations [40].

Severe trauma is another clinical condition commonly associated with DIC. Systemic cytokine patterns in patients with severe trauma have been shown to be virtually identical to those observed in septic patients [41]. In several cases it might be difficult to differentiate DIC from the coagulopathy induced by massive blood loss and by the dilutional coagulopathy manifested as a result of massive transfusion or infusion of large volumes of crystalloids that may occur in the first hours following a major trauma.

Pregnancy is also associated with a risk for hemorrhagic events and obstetrical syndromes that may develop into DIC. During pregnancy, DIC is a rare and unique entity. It is always secondary to an underlying disease or complication and subsides only when the underlying disease resolves. DIC can result from complications unrelated to pregnancy such as sepsis or trauma, but it is also associated with specific pregnancy complications including: 1) acute peripartum hemorrhage (uterine atony, cervical and vaginal lacerations, and uterine rupture), 2) placental abruption; 3) pre-

eclampsia/ eclampsia/HELLP syndrome; 4) retained stillbirth; 5) septic abortion and intrauterine infection; 6) amniotic fluid embolism; and 7) acute fatty liver of pregnancy [42].

DIC is also associated with liver pathology. The physiology of the hemostatic system is intricately linked to normal liver function and overly complicated derangements of hemostasis occur in patients with severe liver disease and liver transplantation. The hemostatic abnormalities in patients with hepatic failure or in those that have undergone liver surgery are similar to those in DIC and it is difficult to distinguish whether or not DIC contributes to hemostatic derangements associated with hepatic pathology [43].

For other underlying conditions (Table 1), DIC is a relatively infrequent complication. In most situations, the severity of the associated systemic inflammatory response in combination with specific circumstances, such as concomitant infections, will determine whether severe systemic coagulation activation will occur.

CLINICAL MANIFESTATIONS

Clinical features

The presenting symptoms of patients with DIC vary from asymptomatic patients to severe multiorgan dysfunction related to thrombotic and/or bleeding events and related thrombotic microangiopathy and hemolysis.

Observed clinical manifestations mainly depend on the nature and severity of the underlying disease and the grade of deregulation of coagulation pathways and so DIC may present as either Latent/chronic/compensated or overt. In latent, chronic or compensated DIC the hemostatic dysfunction is often subtle and/or compensated and the clinical presentation is often

Table 1. *Clinical conditions most frequently associated with DIC.*

Condition	Examples	Impact of precipitating condition
Severe infectious diseases	Gram-positive or -negative organisms, malaria, hemorrhagic fevers	Microvascular thrombosis may contribute to vital organ failure (e.g. acute kidney failure)
Malignancy	Solid tumors (e.g., adenocarcinomas lung, breast, stomach, prostate, pancreas, ovary, biliary tract) Hematological malignancies (e.g. APL, monocytic leukemia, lymphoproliferative and myeloproliferative disorders)	Primarily thrombotic consequences/VTE Severe thrombocytopenia and factor deficiency may lead to bleeding
Trauma	Multitrauma Brain injury Burns	Primary feature is acute bleeding, followed by thrombosis
Obstetrical complications	Abruptio placentae Amniotic fluid embolism Intraamniotic infection	Profuse bleeding in combination with thrombotic complications
Vascular malformations	Kasabach-Merrit syndrome Giant hemangiomas Other vascular malformations Large aortic aneurysms	Bleeding primarily with severe thrombocytopenia and hypofibrinogenemia
Intravascular hemolysis	Snake/insect bites ABO incompatible transfusion	
Severe immunological reactions	Transfusion reaction	
Heatstroke		Thrombotic features more common than bleeding
Post–cardiopulmonary resuscitation		Thrombosis is a greater risk than bleeding
Other	Prosthetic devices, liver failure	

subacute. In such cases it is common that the thrombotic risk is greater than the bleeding risk, whereas in overt DIC bleeding disorders are a more characteristic finding. Clinical manifestations of patients with DIC are the result of multi-organ dysfunction due to either microvascular thrombosis and hemolytic anemia or thrombotic or bleeding events (DVT, PE, etc.). Common findings are summarized in Table 2.

Classification of clinical DIC types

Classifying DIC types based on differences in pathogenesis is important in order to understand the diversity of DIC and to make early diagnosis of DIC and plan for treatment. A major pathogenetic factor in DIC is marked activation of coagulation and is common to all DIC types, but other aspects of the pathogenesis (especially the degree of fibrinolytic activation) differ considerably depending on the underlying disease. PAI regulates the degree of fibrinolytic activity and is a crucial factor in characterizing DIC [35].

Suppressed-fibrinolytic-type DIC (DIC with suppressed fibrinolysis)

DIC with suppressed fibrinolysis is typically seen in sepsis. The fibrinolytic inhibitory factor PAI is markedly increased and therefore fibrinolysis is strongly suppressed, the dissolution of multiple microthrombi is more difficult, and as a result of microcirculatory impairment, severe organ dysfunction may occur. However, bleeding complications are relatively mild [35].

Table 2. *Organ Dysfunction Associated with Severe DIC.*

Organ	Manifestation
Skin	Purpura, bleeding from injury sites, hemorrhagic bullae, focal necrosis, acral gangrene
Cardiovascular	Shock, acidosis, myocardial infraction, cerebrovascular events, thromboembolism in all types and caliber blood vessels
Renal	Acute renal insufficiency (acute tubular necrosis), oliguria, hematuria, renal cortical necrosis
Liver	Hepatic failure, jaundice
Lungs	Adult respiratory distress syndrome, hypoxemia, oedema, hemorrhage
Gastrointestinal	Bleeding, mucosal necrosis and ulceration, intestinal ischemia
Central nervous system	Coma, convulsions, focal lesions, bleeding
Adrenals	Adrenal insufficiency (hemorrhagic necrosis)

Enhanced-fibrinolytic-type DIC (DIC with enhanced fibrinolysis)

DIC with enhanced fibrinolysis is typically seen in APL, abdominal aortic aneurysm, and prostate cancer and is associated with excessive fibrinolysis corresponding to coagulation activation. Fibrinolysis is strongly activated, with no elevation in PAI, thrombi are more easily dissolved, and bleeding symptoms tend to be severe. Organ dysfunction is less common [35].

Balanced- fibrinolytic-type DIC (DIC with balanced fibrinolysis)

DIC with balanced fibrinolysis is common in solid cancers in which case bleeding and organ symptoms are relatively uncommon except in advanced cases.

Phenotypic classification of DIC

Moreover, the 2014 International Society of Thrombosis and Hemostasis (ISTH) harmonized guidelines distinguish DIC types based on clinical phenotype [35,44].

Asymptomatic type DIC

Non-symptomatic DIC is seen in variable underlying diseases and is associated with low grade fibrinolysis and/or hypercoagulation.

Bleeding type DIC

In this form of DIC the predominant mechanism is hyperfibrinolysis and is typically seen in leukemias, obstetric complications and aortic aneurysms.

Massive bleeding type DIC

Massive bleeding type DIC occurs when hypercoagulation and hyperfibrinolysis are equally met and is observed in patients who exhibit marked consumption of coagulation factors and excessive bleeding after major surgery or in those with obstetric complications. It can be fatal if not acutely and effectively managed.

Organ failure type DIC

Organ failure type DIC occurs when hypercoagulation is remarkable and dominant and the main symptom is organ failure due to microthrombi. This form of DIC is

often observed in patients with infection, particularly sepsis.

DIAGNOSIS

Laboratory tests

There is no single laboratory test that can establish or rule out the diagnosis of DIC. Thus, it is of utmost importance to assess thoroughly the clinical presentation of the patient, taking into account the underlying condition and all available laboratory results. Moreover, since DIC is an evolving process, laboratory test values are a snapshot of this dynamic state and must be regarded as such. In addition, in some cases the underlying causative condition or even unrelated co-morbidities of the patient might affect laboratory values assessed for the evaluation of DIC severity. Hematologic malignancies that affect the platelet number regardless of DIC severity or coagulation time prolongation in preexisting hepatic dysfunction are representative examples. However, a combination of tests, when performed regularly in a patient with a clinical condition known to be associated with DIC, can be used to diagnose the disorder with reasonable certainty in most cases.

Laboratory studies used in diagnosis and evaluation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) or platelet count, provide important evidence of the grade of coagulation factor consumption and activation. The laboratory abnormalities detected, in decreasing order of frequency, are thrombocytopenia, elevated fibrin degradation products, prolonged PT, prolonged aPTT, and low fibrinogen.

Platelet count

Low platelets or a rapidly progressing thrombocytopenia is a key finding in DIC. Moderate (< 100,000/ mm^3) to severe thrombocytopenia (50,000/ mm^3) is seen in the majority of patients and those with <50,000 have a 4-5-fold increase in bleeding complications compared to those with a normal platelet count. It is a sensitive but not specific finding of DIC. Thrombocytopenia is seen in about 98 % of cases, with a platelet count of <50,000/ mm^3 in about half of the cases. On the other hand, as mentioned above a low or decreasing platelet count is not specific for DIC since conditions associated with DIC such as acute leukemia and sepsis can also present with thrombocytopenia in the absence of DIC.

Fibrin degradation products and D-dimers

Fibrin degradation product (FDP) is a measure of increased fibrinolytic activity, which is also increased in DIC. FDPs may be detected by specific enzyme-linked immunoabsorbent assays or by latex agglutination assays. FDPs and D-dimers should not be considered as stand-alone tests, but as a useful indicator of DIC when there is an elevation in D-dimer levels with concomitant falls in the platelet count and changes in coagulation times. The specificity of elevated levels of FDPs is limited and many other conditions, such as trauma, recent surgery, inflammation, or venous thromboembolism are associated with elevated FDPs. Soluble fibrin monomer measurements offer theoretical advantages in DIC in reflecting thrombin activity on fibrinogen and are one of the best parameters for detection of developing DIC. However, a major problem remains, that of reliable quantification, with wide discordance reported.

PT and aPTT

Both PT and aPTT are reported prolonged in about 50 % of DIC cases and this is attributed to the consumption of coagulation factors. Prolongation of PT and aPTT can also be detected in impaired synthesis of coagulation factors and in massive bleeding [44,45]. At the same time, at least in half the patients with DIC, PT and aPTT are found normal or even shortened due to the presence of circulating activated clotting factors like thrombin or Xa. Thus, a normal PT or aPTT does not exclude DIC and repeated monitoring is required [46].

Fibrinogen

Measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC but in fact is not helpful in most cases [47]. Fibrinogen acts as an acute –phase reactant and despite ongoing consumption, plasma levels can remain well within the normal range for a prolonged period. In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28% and hypofibrinogenemia was detected in very severe cases of DIC only [47]. Fibrinogen levels can be normal in as many as 57% of patients [48].

Blood film

The evaluation of the blood film of a patient with DIC can confirm the platelet count when there is doubt, identify pathological cells (e.g. leukemic or lymphomatic cells) in case of underlying hematological malignancy and detect fragmented red blood cells. Fragmented red blood cells are the result of hemolysis due to thrombotic

microangiopathy, and although reported in patients with DIC, rarely constitute > 10% of the red blood cells. The finding of fragments is neither sensitive nor specific to DIC. When they are seen in increased numbers, other potential diagnoses, such as thrombotic thrombocytopenic purpura and other causes of thrombotic microangiopathy should be considered.

Specialized tests

In a specialized setting, molecular markers for activation of coagulation or fibrin formation may be the most sensitive assays for DIC [6]. A number of clinical studies show that the presence of soluble fibrin in plasma has a 90-100% sensitivity for DIC but, unfortunately, a relatively low specificity. The dynamics of DIC can also be judged by measuring activation markers that are released upon the conversion of the coagulation factor zymogen to an active protease, such as prothrombin activation fragment F1+2. Indeed, these markers are markedly elevated in patients with DIC, but again, the specificity is not adequate.

Levels of antithrombin activity decrease in severe sepsis [49] and are associated with poor survival [50]. The Japanese Association for Thrombosis and Hemostasis (JSTH) proposed in 2018 new DIC diagnostic criteria which include antithrombin activity [51]. Previously, in 2016 Iba et al had proposed a revision of the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria using antithrombin activity [52].

Evidence also suggests that serum levels of thrombomodulin, a marker for endothelial cell damage, correlate well with the clinical course of DIC, the development of multiple organ dysfunction syndrome (MODS), and mortality in septic patients. Thrombomodulin is elevated in DIC, and this elevation not only correlates well with the severity of DIC but also can serves as a marker for early identification and monitoring of DIC [53].

Thromboelastography (TEG) is a point-of-care test that evaluates the entire process of clot formation and dissolution. TEG has been reported as useful in the diagnosis of coagulation abnormalities in sepsis patients and may be associated with clinical prognosis [54]. The advantage of this test is that it enables bedside performance and can be used in acute care settings.

Scoring Systems

Multiple scoring systems have been developed in Japan, Italy and the United Kingdom for the diagnosis of DIC. The major concern that arises with the use of these scoring systems is their ability to diagnose non-overt DIC, as well as initial stages of acute DIC.

The scoring system of The International Society on Thrombosis and Hemostasis (ISTH) is widely used for the diagnosis of overt DIC [55,56,57,58] (Table 3). It is a five-step diagnostic algorithm to calculate a DIC score based on simple laboratory results. For a diagnosis of DIC, a score of ≥5 is required regardless of the etiology of DIC. The score has a sensitivity of 93% and specificity of 98% [59,60] and a strong correlation between an increasing score and mortality has been reported. The severity of DIC according to this scoring system is a strong predictor for mortality in sepsis [61].

As concern pregnancy, none of these scores is adjusted for the physiologic hemostatic changes occurring in pregnancy. Based, on this consideration Erez et al. [62], developed a pregnancy modified DIC score by using only three components of the ISTH DIC score (platelet count, fibrinogen concentrations and the PT difference) (Table 4) and showed that at a cutoff of ≥26 points had a sensitivity of 88%, a specificity of 96%, a positive likelihood ratio of 22, and a negative likelihood ratio of 0.125 for the diagnosis of DIC.

Table 3. *Scoring algorithm for the diagnosis of DIC.*

Platelet count, ×109/L
>100 = 0
<100 = 1
<50 = 2
Level of fibrin markers (e.g. D-dimer, fibrin degradation products)
No increase = 0
Increased but <5x upper limit of normal = 2
Strong increase (≥5x upper limit of normal) = 3
Prolonged prothrombin time*
<3 s = 0
≥3 s but<6 s = 1
≥ 6 s = 2
Fibrinogen level
>1.0 g/L = 0
≤1.0 g/L = 1

*If prothrombin time values are only available as INRs, an INR value of >1.3 or >1.5 will generate 1 or 2 points respectively (assuming the International Sensitivity Index value of the prothrombin reagents used is close to 1).

Table 4. *Comparison of the ISTH DIC score and the pregnancy-modified ISTH DIC score.*

P arameters	ISTH score	Pregnancy Modified ISTH score
Platelet count($10^{9/L}$)		
>185000		0
>100000	0	1
50000-100000	1	2
<50000	2	1
PT difference(s)		
>1.5	N/A	25
1-1.5	N/A	12
0.5-1	N/A	5
<0.5	N/A	0
Prolonged PT(s)		
≥6	2	N/A
≥3 to <6	1	
<3	0	
Fibrinogen (g/L)		
<1	1	
≥1	0	
≤3		25
3-4		6
4-4.5		1
≥4.5		0
Fibrin split products		
No increase	0	N/A
Moderate increase	2	
Strong increase	3	
Definition of DIC	Score >5 compatible with overt DIC	Score >26 compatible with overt DIC

Differential Diagnosis

The differential diagnosis of DIC is broad and includes other causes of consumptive coagulopathies, such as trauma and major surgery. In addition, severe liver disease can result in markedly reduced production of coagulation factors and inhibitors. Thrombocytopenia may also occur in this setting secondary to splenic sequestration, resulting in an overall clinical picture quite similar to DIC.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are thrombotic microangiopathies that share similar clinical features with DIC, but in contrast to DIC, the mechanism of thrombosis is not via the TF/factor VIIa pathway. Results of blood coagulation assays in TTP and HUS are normal [63] and thrombosis arises from direct platelet activation, usually as a result of widespread endothelial damage or an inherited or acquired impairment of ADAMTS13, a protease that normally cleaves von Willebrand factor (vWF), which results in ultra-large vWF polymers (ULVWF) that agglutinate platelets, leading to thrombosis and shearing of red blood cells [64]. Moreover, TTP and HUS are associated with microangiopathic hemolytic anemia, whereas in DIC hemolysis is not a feature.

Other thrombotic microangiopathies include chemotherapy-induced or stem cell transplant–associated microangiopathy and HIV-induced TTP [65].

Thrombocytopenia is present in both DIC and immune thrombocytopenia (ITP). However, ITP is distinct from DIC in terms of its pathophysiologic mechanism and does not involve coagulation activation, microangiopathic hemolytic anemia or presence of typical schistocytes in blood films.

Heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) is another clinical entity with a presentation similar to that of DIC but microangiopathic hemolytic anemia is absent, and the history of heparin administration is a weighing factor for differential diagnosis. A subgroup of patients who have received heparin develop antibodies against platelet antigens (PF4) which leads to thrombocytopenia derived from platelet destruction and in some cases thrombosis as a result of platelet activation. In HITTS, the plasma PT, the aPTT, and the fibrinogen levels are normal [66].

MANAGEMENT

General principles of DIC management

Managing thrombotic and hemorrhagic risk in DIC is a challenge for the clinical physician. Replacement of deficient hemostatic components is not a straightforward decision to make in most cases and the synchronous configuration of both thrombotic and fibrinolytic pathways demands a complex therapeutic algorithm. Multiple factors should be taken under consideration, such as the etiology of DIC,

the thrombotic versus hemorrhagic manifestations or risk of the specific patient, laboratory test values, co-morbidities, and estimated time to treatment of underlying etiologic condition.

DIC is always secondary to an underlying condition and thus the cornerstone of management is the treatment of etiology [67]. This is more profound in obstetrical DIC, where the coagulation disorder is often resolved by the removal of the placenta. Similarly, in cases of infectious sepsis, appropriate antibiotics and/or surgical drainage are necessary [4] whereas in cancer patients, treatment should not be delayed [68].

Prophylactic and therapeutic anticoagulation

Based on the previous knowledge of the partial inhibition of coagulation activation [69] by heparin, its benefit in DIC was early investigated. Heparin use results in restraining excess effects of thrombin [70] and improving laboratory values [71]. Although critically ill patients and patients with sepsis have been found to benefit from prophylactic use of heparin [72,73] and its use has been standard of care, there is no large randomized trial demonstrating the clinical impact of heparin use in patients with DIC. A meta-analysis of trials of anticoagulant therapy in patients with sepsis, showed a significant reduction in mortality in the population with sepsis associated DIC who received any of the examined treatments as compared to those who did not receive any anticoagulant treatment [74].

Choice of heparin has been a debatable issue. A small, randomized trial showed that low molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH) for treating DIC [75] and thus it is more commonly suggested, except in cases with high risk of bleeding and renal failure, where UFH is preferred due to its easier reversibility [76]. In general, thromboprophylaxis is indicated in DIC, but should be paused or avoided in bleeding or high- bleeding risk patients or if platelet count drops below the threshold of 20 x 10^9/l [58].

Cancer-mediated prothrombotic state is well clinically established. Cancer patients with DIC are at substantial risk of several types of thrombosis, not only due to pathogenetic mechanisms described, but also to other contributing factors, such as recent surgery, immobilization, advanced age, indwelling catheters that may favor thrombosis, and chemotherapy- induced endothelial damage. Therefore, thrombosis prevention with unfractionated or LMW heparin has become customary in patients with malignancies and signs of a procoagulant condition [77].

APL is a high bleeding risk hematological malignancy, and the concern of hemorrhagic death does not allow indiscriminate use of anticoagulation [78]. As a result, caution is advised regarding thromboprophylaxis, and prophylactic platelet transfusion is suggested to maintain platelet counts above 30 x 10^9/l [79].

As obstetric DIC primarily manifests with bleeding, the role of UFH or LMWH is unclear and should be reserved for patients in whom thrombosis is the dominant manifestation, such as amniotic fluid embolism or mismatched blood transfusion [58,80].

Optimal timing for the initiation of pharmacological thromboprophylaxis is often difficult for trauma DIC, but it is generally suggested within 24 hours after bleeding control or at 48 hours of hospitalization to reduce venous thromboembolism (VTE) risk [81]. Therapeutic heparin use in DIC is restricted to patients with VTE or severe thrombotic manifestations, such as acral ischemia, and the use of LMWH is preferred to UFH [57,58,82]. In patients with thrombosis and concomitant bleeding, a vena cava filter should be considered in parallel with platelet and FFP transfusion strategies, permitting the use of therapeutic LMWH [83].

Direct oral anticoagulants (DOACs) specifically inhibit thrombin and factor X, hence theoretically their use in DIC would be reasonable. Nevertheless, current literature data consists only of case reports [84].

Platelet transfusion

Platelet or plasma transfusion should not be started based on laboratory results alone. Platelet transfusion is recommended under the threshold of 50 x10^9/l in DIC patients with major bleeding, such as in a perioperative period, obstetric DIC complicated by postpartum hemorrhage. In severe trauma with concomitant ongoing bleeding or trauma brain injury, maintenance of a platelet count above 100 x10^9/l is advised [85].

In cancer-DIC or patients with minor or no bleeding, a markedly lower threshold of 20 x10^9/l for platelet transfusion is advised [58,83]. In APL patients, given the high risk of hemorrhagic mortality during early induction, ISTH suggests a higher transfusion threshold of platelet count < 30 ×10^9/L [79].

In patients undergoing surgery or invasive procedures, transfusions of one to two doses of platelets are suggested if the platelet count is less than 30 x10^9/l in APL, and less than 20 x10^9/l in other malignancies [76].

Plasma /Cryoprecipitate /Fibrinogen concentrate transfusions.

To support coagulopathy in patients with DIC and active bleeding or prolonged aPTT and/or PT values (> 1.5 times normal), fresh frozen plasma transfusions are indicated (15-30ml/kg) [32,58]. Careful clinical and laboratory monitoring is required for dose adjustments. For patients in danger for volume overload, smaller volumes of prothrombin complex concentrates (PCC) might be of use. However, most PCC contain the vitamin K-dependent FII, FVII, FIX and FX, but lack important coagulation factors, e.g. FV, and no specific dosing strategies exist [58,82].

Generally, it is well established that fibrinogen levels <100 mg/dL is a critical threshold to treat hypofibrinogenemia [86]. As far as DIC is concerned, in bleeding patients and fibrinogen levels <150 mg/dL and in women with concomitant postpartum hemorrhage with fibrinogen levels <200mg/dL, administration of fibrinogen is indicated either as fibrinogen concentrate or as cryoprecipitate. Administering fibrinogen concentrate 30 mg/kg, the level of fibrinogen will increase 100 mg/dL, whereas for cryoprecipitate, two pools are recommended to increase fibrinogen levels [32,58].

In trauma induced DIC with substantial bleeding, where fibrinolysis is mostly prominent, either plasma transfusion is recommended to maintain PT and APTT <1.5 times the normal control or treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding accompanied by a plasma fibrinogen level of less than <150 mg/dL. Initial fibrinogen supplementation of 3–4 g fibrinogen concentrate is equivalent to 15–20 single donor units of cryoprecipitate. In a massive bleeding setting, plasma (FFP or pathogen-inactivated plasma) is advised in a plasma–RBC (red blood cell) ratio of at least 1:2 [85].

FVIIa binds to TF at the site of endothelial damage and their complex is necessary to initiate hemostasis [87]. In concentrations higher than normal, FVIIa can activate FX on activated platelets as well, leading to an excess thrombin production [88]. In patients with severe overt DIC and hemorrhage refractory to FFP, PCCs and platelet concentrates, treatment with recombinant FVIIa (rFVIIa) is an additional option. This option is exceptionally used in the management of obstetrical DIC secondary to placental abruption or amniotic fluid embolism with severe peripartum hemorrhage or major bleeding and traumatic coagulopathy persistent despite all other attempts to control bleeding and best-practice use of conventional hemostatic measures [89]. Treatment with rFVIIa is commonly at a dose of 90-100 μg/kg. However, this treatment should be used with caution and in selected cases because of the increased thromboembolic risk [90].

Anticoagulant factor concentrates.

The use of different agents restoring dysfunctional anticoagulant pathways in patients with DIC, has been the center of attention early on. Antithrombin concentrate has been available for more than 30 years, but large multicenter studies have failed to demonstrate survival benefit [4,91].

Clinical efficacy of activated protein C (APC) in sepsis was assessed in a large, randomized trial [92] and a post hoc analysis demonstrated its benefit specifically in patients with overt DIC [61]. Nevertheless, afterwards, the ADRESS study, showed that in patients with low mortality risk (APACHE score <25 or single organ failure), APC had no significant benefit and resulted in more severe bleeding episodes [93]. With the increasing uncertainty about efficacy and the concerns about bleeding risk, the PROWESS-SHOCK trial was initiated to reexamine the risk-benefit profile of the drug. This trial, involving 1697 patients, failed to show any benefit in mortality compared to a placebo, even in patients with severe protein C deficiency. Following these results, the product was withdrawn from the market worldwide [6].

Thrombomodulin forms a complex with thrombin and subsequently inhibits its activity. Thrombomodulin recombinant soluble form (recTM) is extensively studied in Japan, for DIC associated with sepsis or cancer [58]. In a recent randomized trial, including 816 patients with mean APACHE II score approximately 22 in both drug and placebo groups, only minor reduction in mortality was demonstrated, though with notably no increase in bleeding risk [94].

TFPI inhibits factor Xa directly and is the main inhibitor of the TF/FVII catalytic complex and thus it would be an excellent target for DIC treatment. Nevertheless, the phase 3 multicenter OPTIMIST trial failed to show a survival benefit in patients with severe sepsis receiving recombinant TFPI compared to placebo [95].

Anti-fibrinolytics

As suppression of fibrinolysis is a contributing factor in sepsis DIC, the use of anti-fibrinolytics is generally not reasonable [32]. Although these agents were advocated for the treatment of hyperfibrinolytic DIC

of APL before the era of all-trans retinoic acid, a larger retrospective study did not demonstrate clinical benefit [96]. Moreover, the PETHEMA group study failed to identify a clear reduction on hemorrhagic incidents with systematic tranexamic acid prophylaxis along with induction therapy but demonstrated a higher incidence of thrombotic events [97]. In summary, antifibrinolytic agents are not routinely recommended even for hyperfibrinolytic DIC and may be deleterious in the other types. However, if therapy resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered [76]. Especially in severely bleeding trauma patients, tranexamic acid is only found to be beneficial if administered within 3 hours after injury [85].

The treatment algorithm of DIC is depicted in figure 1 and molecular targets of therapeutic interventions in figure 2.

Prognosis

Prognosis of patients with DIC depends on the severity of the coagulopathy and on the status of the underlying condition that led to the manifestation of DIC. Assigning numerical figures to DIC-specific morbidity and mortality is difficult. The following are examples of mortality rates for diseases complicated by DIC:

- Idiopathic purpura fulminans associated with DIC have a mortality rate of 18%.
- Septic abortion complicated by clostridial infection and septic shock associated with severe DIC has a mortality rate of 50%.
- In the setting of major trauma, the presence of DIC approximately doubles the mortality rate [50,98].

In general, if the underlying condition is self-limited or can be appropriately managed, DIC will disappear, and coagulation will be gradually restored. A patient with acute hemorrhagic DIC that is associated with metastatic gastric carcinoma most probably has a lethal condition that does not alter patient demise, regardless of the applied treatment. On the other hand, a patient with acute DIC associated with placental abruption needs quick recognition and obstetric treatment; in this case DIC will be resolved with the treatment of the obstetric catastrophe.

DIC has been shown to be an independent predictor of mortality in patients with sepsis and severe trauma [99-103). The presence of DIC may increase the risk of

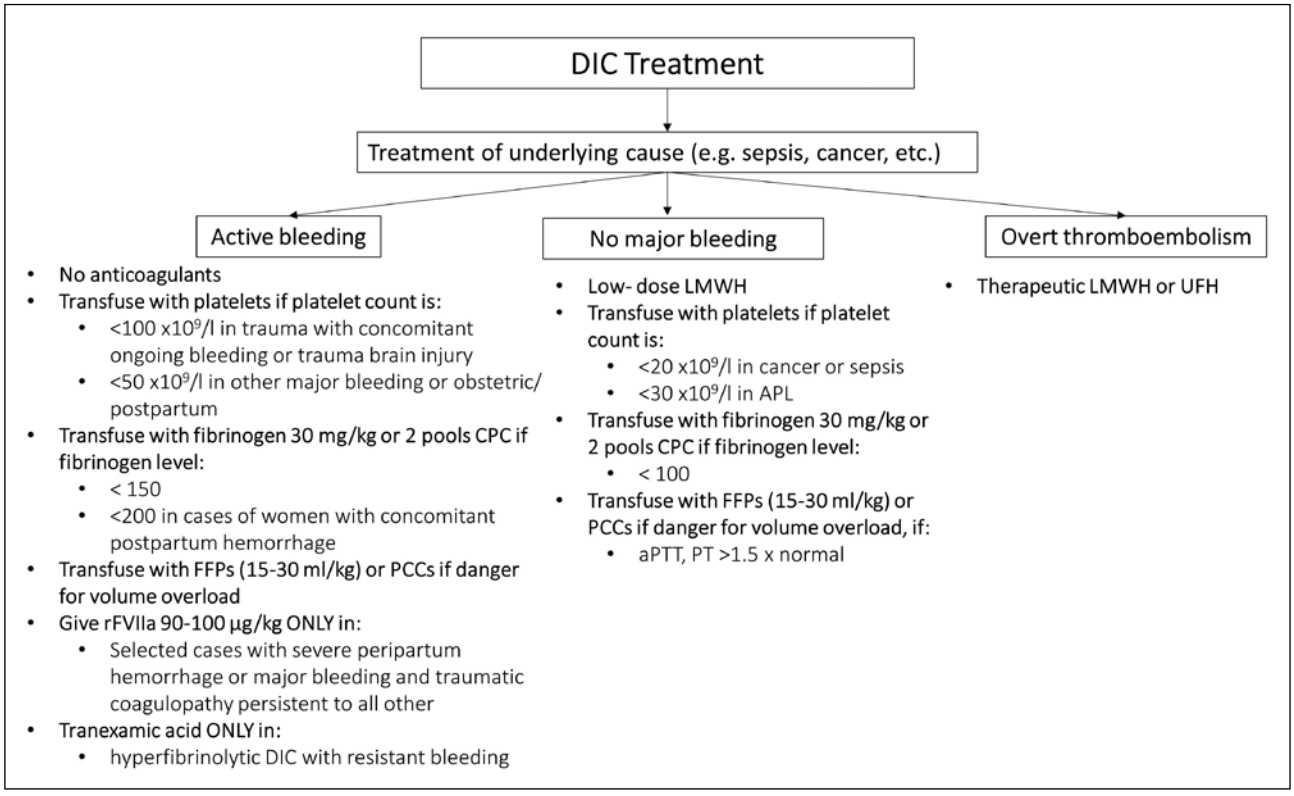

Figure 1. DIC treatment algorithm.

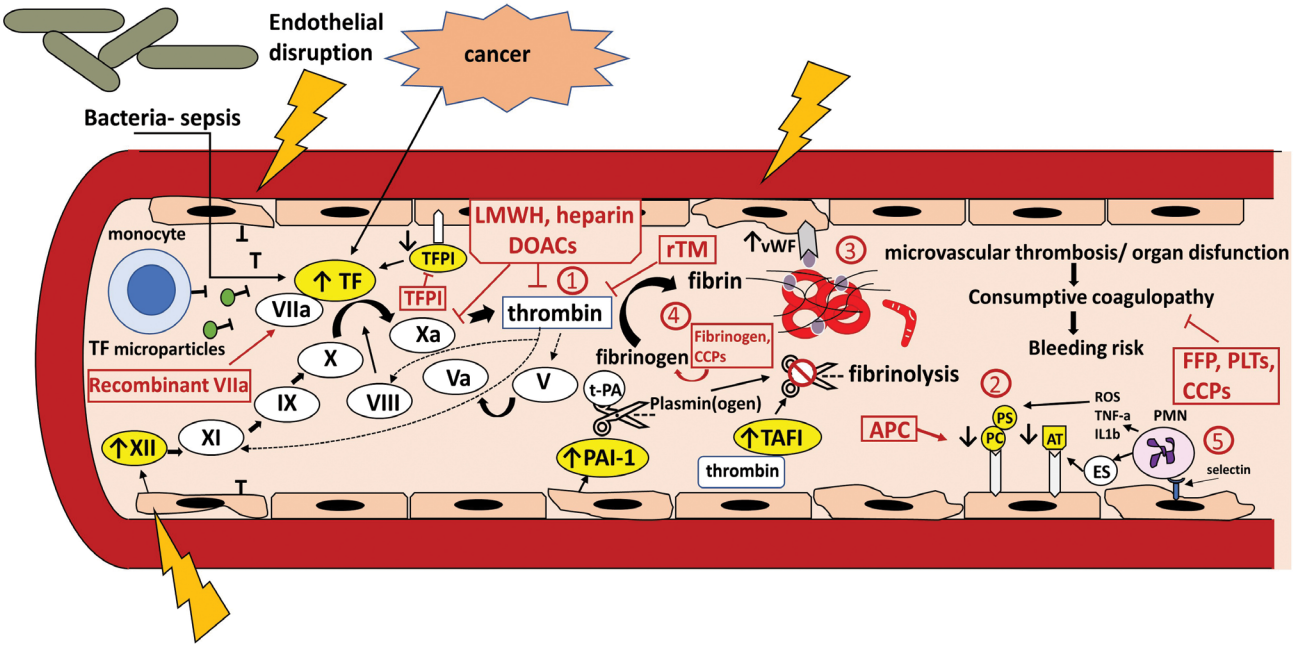

Figure 2. DIC pathophysiology. Pathophysiology of DIC is characterized by: 1. Excess thrombin generation driven by TF, 2. Consumptive coagulopathy and deficiency of natural anticoagulants (protein C, S), 3. Platelet activation enhanced by endothelial damage, pathogens and proinflammatory molecules 4. Defective fibrin degradation and 5. Immune-mediated thrombosis. Therapeutic measures target distinct parts of these pathways. Heparin, LMWH, DOACs, TFPI and rTM act by inhibiting excess thrombin and activated factor Xa. Platelets, FFPs, CCPs and fibrinogen partially restore consumptive coagulopathy in patients with high bleeding risk. APC used to substitute protein C is currently withdrawn from the market. rFVIIa binding to TF to initiate hemostasis, is only used in DIC with persistent bleeding.

death by a factor of 1.5 to 2.0 according to numerous studies. A study utilizing the JAAM diagnostic criteria for DIC, showed that septic patients with DIC had a higher mortality than trauma patients with DIC did (34.7% vs 10.5%) [104].

DISCUSSION

DIC is a common, multifactorial, complex consumptive coagulopathy, endangering patients of all races, gender and ages with different underlying conditions and increasing their mortality. Sepsis, cancer, major trauma, and obstetric emergencies are four of the main underlying conditions associated with DIC. Clinical approach demands understanding of the pathogenetic mechanisms, identification of the underlying causative factor, thorough physical examination, and regular laboratory tests to evaluate the thrombotic versus bleeding risk of the patient and the severity of their clinical status, and choice of the appropriate supportive measures.

Thrombin generation, deficiency of natural anticoagulants, platelet activation, defective fibrinolysis and immune-mediated thrombosis are the major pathogenetic mechanisms. The grade of dysregulation of these pathways and the capability of repairing mechanisms to restore coagulation balance will define the spectrum of clinical manifestations exhibited by patients with different underlying conditions and lead to distinct phenotypes. These different subtypes of DIC phenotype are one of the reasons that this clinical entity is a challenge for the physician in terms of diagnosis but also management.

Laboratory tests are mandatory for the diagnosis and regular follow up is needed to assess both the grade of the coagulopathy as well as the effectiveness of treatment. Different scoring systems assess the probability and/or severity of DIC and can be easily incorporated in routine clinical practice. Current therapeutic interventions are mostly supportive and difficult to manage due to simultaneous existence of both bleeding and thrombotic risk, limited availability of real time evaluation of measurements depicting the severity of coagulopathy and the multifactorial pathogenesis of DIC which stimulates a vicious cycle. This explains why no single treatment option has proven to be adequate to restrict the phenomenon once initiated. Our interventions should be carefully justified and there should be constant re-evaluation of clinical and laboratory parameters to guide our therapeutic strategy.

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Acute non-variceal upper gastrointestinal bleeding: Changes and advances over the past years

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Abstract

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is an emergent situation, with significant morbidity and mortality. The initial approach to the patient's resuscitation includes intravenous fluids and red blood cell transfusions where needed, followed by proton pump inhibitors (PPIs) administration. Esophagogastroscopy should be performed within 24 hours from admission, while earlier endoscopy could be considered in patients at high risk, such as hemodynamically unstable patients. Endoscopic intervention is indicated for high risk non-variceal bleeding (active bleeding, non-bleeding visible vessel). The current article reviews up-to-date strategies for patient's risk stratification, initial management, causes of ANVUGIB, timing of endoscopy, role of proton pump inhibitors and antithrombotic agents.

Key words: *Acute non-variceal upper gastrointestinal bleeding; (ANVUGIB); peptic ulcer; proton pump inhibitors (PPIs); endoscopy; hemostasis*

INTRODUCTION AND EPIDEMIOLOGY

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB), despite advances in diagnosis and management, remains a life-threatening emergency with considerable morbidity and mortality [1]. The incidence of acute upper gastrointestinal bleeding is approximately 100 cases per 100,000 inhabitants and appears to be decreasing in recent years, due to the reduction in the incidence of peptic ulcer bleeding [2].

Although, peptic ulcer (figure 1a-b) remains the most common cause of acute upper gastrointestinal bleeding its incidence has decreased [2]. In general, the prevalence of *Helicobacter pylori* (*H. pylori*) infection has been declining and due to successful eradication regimens, thus, *H. pylori* related peptic ulcer disease is less frequent today [3]. In addition, prophylactic co-administration of proton pump inhibitors (PPIs) to users of aspirin and/or nonsteroidal anti-inflammatory drugs (NSAIDs) and/or use of selective COX-2 inhibitors, in some cases, have led to the reduction in the incidence of peptic ulcer related bleeding [4].

On the other hand, other causes are being increasingly encountered like esophagitis, neoplasms, angiodysplasias, Dieulafoy's lesions etc. [5] (figure 1c-f). This increase is mainly due to the increased use of antithrombotic medication of the elderly population that causes acute bleeding from a pre-existing non-bleeding lesion [5]. Nowadays, there is evidence that bleeding episodes are less severe, but the patients are more frail and older with more comorbidities [6].

In more than 80% of the cases, bleeding is self-limiting, while in less than 20% we have continued or

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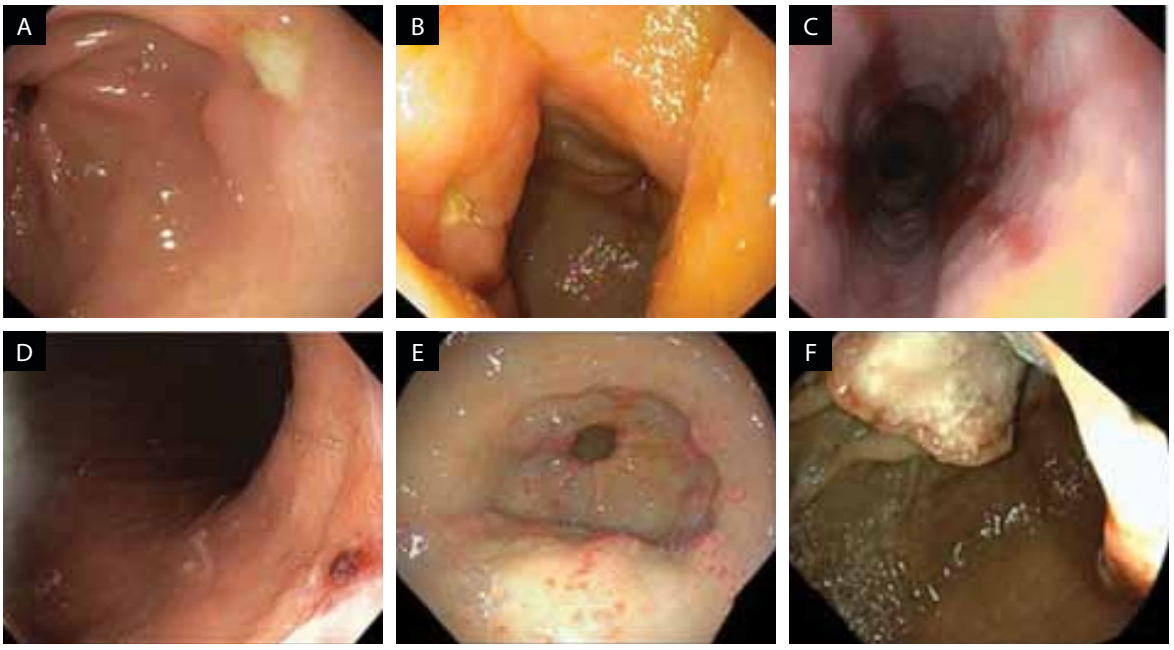

Figure 1. Causes of ANVUGIB. 1A, 1B: Peptic ulcer, 1C: Esophagitis, 1D: Dieulafoy's lesion, 1E: Angiodysplasias, 1F: Neoplasm.
Source: Personal records.

recurrent bleeding (95% of recurrences occur in the first three days from the onset of bleeding) [7]. With advances in endoscopic treatment, less than 3% of patients will require emergency surgical hemostasis [7]. Shock on admission, low admission hemoglobin levels, active spurting bleeding on endoscopy, ulcers of the posterior-lower wall of the duodenum and large ulcers are associated with an increased probability of recurrence of bleeding in patients with ANVUGIB [8].

Despite advances in the diagnostic and therapeutic field, mortality has not been considerably reduced and remains static, at around 5%, in recent years [9]. Mortality is mainly attributed to the accompanying diseases that are common in these patients and not to the blood extravasation itself, which is being treated [10]. Less than 20% of deaths are directly associated with massive blood loss [10]. There is also evidence that weekend admission is associated with a significant increase in mortality in patients with ANVUGIB, emphasizing the importance of careful management of these patients, regarding not only endoscopy but also supportive care [11].

Today, patients with ANVUGIB are older (average age 65-70 years) and the increased incidence of bleeding is mainly due to the increased use of antithrombotic agents and/or NSAIDs [5]. More than 75% of the patients have some co-morbidity, with cardiovascular disease being the predominant one, while over 50% of the patients receive some antithrombotic treatment or combinations and this percentage is constantly increasing [6].

It is important to emphasize that patients hospitalized with ANVUGIB have a substantial 30-day readmission rate following discharge and this is mainly not due to recurrent bleeding but due to other causes, mainly metastatic cancer or cardiovascular disease [12, 13].

Initial management – Principles of treating a patient with upper gastrointestinal bleeding

Clinical assessment of the severity of bleeding and blood loss, placement of wide bore intravenous access and resuscitation remain the cornerstone of management, regardless of the cause of bleeding [14]. After the stabilization of the patient, an endoscopy should be performed which provides diagnosis, treatment, and prognosis [14]. In patients with persisting hypotension, despite fluid resuscitation, intensive care is necessary [14].

Placing a nasogastric catheter (levin) in upper gastrointestinal bleeding for suction and lavage has no significant benefit and is not currently recommended [14]. Differential diagnosis of bleeding between upper and lower digestive tract is mandatory and should be done based on the clinical presentation [14]. Elevated blood urea with normal creatinine is a helpful factor, because it increases in upper gastrointestinal bleeding,

as the protein components of the blood are absorbed in the small intestine and metabolized in the liver to create urea but are lost in colonic bleeding [14].

Risk assessment

As the majority of patients will not develop rebleeding or complications, it is important to stratify patients with ANVUGIB into low or high risk for rebleeding, need for intervention and death, even on admission [15-17]. Various risk assessment scores have been developed and validated, both on admission and before endoscopy (including clinical and laboratory parameters) and later after endoscopy (incorporating also endoscopic findings), like Rockall score, AIMS65 and Glasgow-Blatchford score [15-17]. Pre-endoscopy risk scoring would also enable patients who are at very low risk to avoid admission to hospital (or be discharged earlier) [15-17].

In an international multicenter study these scores have been compared prospectively in 3012 patients [18]. Glasgow-Blatchford score was found more accurate in predicting, in general, need for any hospital-based intervention or death at 30-days in all countries, with a score 0 or 1 being the optimum threshold for identification of patients at low risk and suitable for outpatient management [18]. However, no score had significant predictive value for any separate outcome, including need for endoscopic treatment, rebleeding and mortality; therefore, their clinical utility to direct management of high-risk patients seems limited [18]. Moreover, less than 19% of patients have Glasgow-Blatchford score ≤1, so the majority of patients should be closely monitored in the first days [18].

Based on the available evidence European Society of Gastrointestinal Endoscopy (ESGE) recommends the Glasgow-Blatchford score using a cut-off of ≤1 to identify low-risk patients, who can be safely managed as outpatients [14].

Timing of endoscopy

Early endoscopy (within 24h) has been found more beneficial compared to later endoscopy, in patients with acute gastrointestinal bleeding from previous studies over the past three decades, although it is questionable whether it improves mortality [19,20].

Urgent endoscopy (during the first 6h) has been tried in the past to improve clinical outcome of patients with upper gastrointestinal bleeding, however, no difference in rebleeding and mortality was observed and the effect on the length of hospital varies [21,22]. Urgent endoscopy has not been shown to be better than endoscopy performed within the first 24 hours of hospitalization [21,22].

In a recent nationwide Danish cohort study including 12.601 patients no association between timing of endoscopy and mortality in hemodynamically stable patients with an ASA score (American Society of Anesthesiologists) of 1 to 2 was found [23]. Even in hemodynamically stable patients with an ASA score of 3 to 5, endoscopy 12 to 36 hours after admission to the hospital was associated with lower in-hospital mortality, while in patients with hemodynamic instability, endoscopy 6 to 24 hours after admission to the hospital was associated with lower in-hospital mortality [23].

ESGE guidelines do not recommend urgent endoscopy (≤12 hours) due to lack of improvement in clinical outcome of the patients [14]. Although exact timing of endoscopy is still challenging, endoscopy should be performed after careful and adequate resuscitation and optimum management of underlying comorbidities, on a case-by-case basis, always taking all the necessary precautions and ensuring ideal conditions in terms of equipment and personnel [14].

Pre-endoscopy proton-pump inhibitors

In a previous meta-analysis including six randomized controlled trials (RCTs), PPI treatment initiated before endoscopy at the emergency department led to a reduction of participants with stigmata of recent hemorrhage and requirement for endoscopic therapy during index endoscopy, without affecting clinically important outcomes, namely mortality, rebleeding or need for surgery [24]. As more than two thirds of patients with bleeding suffer from hydrochloric acid secretion related diseases, PPIs from admission are suggested to all patients with ANVUGIB [24].

Endoscopic hemostatic methods

In patients with active bleeding or non-bleeding visible vessel, because of the high probability of rebleeding, endoscopic hemostasis with various methods is important as it reduces the recurrence of bleeding and therefore the need for blood transfusions, length of hospitalization and need for emergency surgical hemostasis [25].

Oozing bleeding, although is considered high-risk for rebleeding, may have been overestimated as, compared with Forrest Ia, Iia and Iib lesions, has a very low rebleeding rate following successful hemostasis [26].

The management of lesions with adherent clot is controversial. Although not fully established, a strategy of careful clot detachment (to avoid bleeding) and adjunctive endoscopic hemostasis, when necessary, is recommended in patients with adherent clot [25]. Lesions with clean base or pigmented flat spots are of negligible risk of rebleeding and do not require endoscopic intervention and are amenable to early discharge [25].

A variety of endoscopic hemostatic methods has been developed and tested during the past years including thermal coagulation methods, mechanical modalities, like through-the-scope clips and bands and injection of various substances, mainly adrenaline solution [27] (figure 2). The best endoscopic hemostatic method depends on the type and location of the lesion, the severity of the bleeding, the endoscopist-nurse experience and the available equipment in each case [27].

Many studies and meta-analyses have shown that endoscopic injections of substances are equivalent to each other, mechanical methods of hemostasis are equivalent to thermal methods, mechanical and thermal methods are superior to endoscopic injections of substances and combination of endoscopic therapies is superior to monotherapy in arresting bleeding and preventing recurrence [28].

Epinephrine injection can be used to temporarily reduce bleeding and aid visualization of the bleeding lesion before the use of another endoscopic modality [28]. Some lesions need specific endoscopic hemostatic methods like argon plasma coagulation for angiodysplasias and band ligation or even radiofrequency ablation for watermelon stomach [30, 31].

During the last decade several new modalities have been introduced in endoscopic hemostasis, mainly hemostatic powders or gels (Hemospray, Purastat, etc..) and over-the-scope clips (or cap-mounted clips). More studies are required to establish their role in the endoscopic management of ANVUGIB [32-34]. Probably, local hemostatic agents may be used as the first line hemostatic method for diffuse bleeding from a tumor, while over the scope clips can be used as rescue therapy for patients with persistent or recurrent bleeding despite initial hemostasis, but further studies are required [35-37].

Attempts have been made by using a through-the-scope Doppler probe before and after endoscopic hemostasis to better assess arterial submucosal blood flow [38]. Although it was found that this technique reduces rebleeding compared to the standard visual inspection, this modality has not gained wide popularity [38].

Performing a second endoscopy in the absence of recurrence (second look endoscopy) is not recommended but should be done when the endoscopist is not satisfied with the applied endoscopic hemostasis [39].

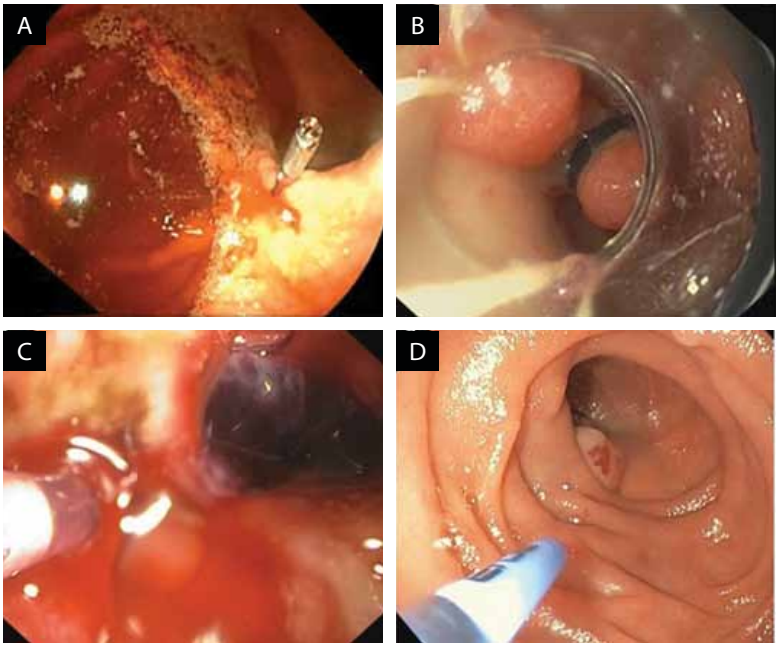

Figure 2. Endoscopic hemostatic methods. 2A: Through-the-scope clip, 2B: Banding, 2C: Adrenaline injection, 2D: Argon plasma coagulation (APC).
Source: Personal records.

Post-endoscopy medical therapy in patients with ANVUGIB

As more than two thirds of patients with bleeding suffer from hydrochloric acid secretion related diseases, PPIs from admission are suggested to all patients with ANVUGIB. It has been suggested that high doses (initially intravenous bolus 80mg and then 8mg/hour for 72 h) achieve faster a higher gastric Ph which would lead to faster ulcer healing and inhibition of pepsin activation, which dissolves the clot (at Ph< 6) [40]. However, in comparative studies and meta-analyses this was not completely confirmed [40]. Nevertheless, in patients at high risk for rebleeding, high doses of PPIs are recommended, given continuously or intermittently [41,42]. Also in a previous study, double oral esomeprazole 40 mg twice daily for two weeks after a 3-day infusion reduced peptic ulcer rebleeding in high-risk patients compared with standard dose once daily [43].

Somatostatin and tranexamic acid have no benefit in non-variceal upper gastrointestinal bleeding and should not be used for the treatment of ANVUGIB outside the context of a randomized trials [44,45].

Blood product transfusions

A more restrictive transfusional approach is recommended for patients with ANVUGIB today [41,42]. A meta-analysis of five RCTs including 1,965 patients with gastrointestinal bleeding revealed significantly lower all-cause mortality and rebleeding rates in patients allocated to a restrictive versus a liberal transfusion strategy, with no difference in risk of ischemic events [46]. A target of maintaining hemoglobin level of 9 mg/dl in patients with coronary disease and 7-8 mg/dl in younger patients without accompanying diseases and especially in patients with liver cirrhosis/portal hypertension is recommended, in order to avoid heart function overload and portal pressure increase in cirrhotic patients [46].

Ongoing or recurrent bleeding

On recurrence of bleeding, re-endoscopy (and endoscopic hemostasis if possible) should be attempted, as it may lead to permanent hemostasis and reduce the need for emergency surgical hemostasis with less morbidity [47]. Use of newer hemostatic modalities, like over the scope clips, may increase the rate of permanent hemostasis [48]. It should be emphasized that a correct assessment of the lesion and the bleeding vessel is crucial and unnecessary repeated endoscopic hemostasis must be avoided, while there should be close co-operation between the endoscopist and the surgeon [47].

In cases of older patients and/or with severe comorbidity, where surgery is accompanied by high morbidity and mortality, selective arterial embolization of the bleeding vessel has given good results. Immediate and permanent cessation of bleeding can be achieved in 85-90% of cases without significant complications [49]. On the other hand, there is no evidence for prophylactic angiographic embolization after initial endoscopic control of bleeding in patients with high-risk peptic ulcers [50].

Negative endoscopy in a patient with upper gastrointestinal bleeding

If there is not a cause of bleeding in the gastroscopy, it is most likely that the cause is in the lower digestive tract and in these cases, in massive bleeding, we proceed to a CT-angiography and in less massive bleedings to an ileocolonoscopy and capsule enteroscopy after complete preparation of the intestine [51]. In some cases, a bleeding lesion in the range of upper GI endoscopy might be missed or not assessed correctly by the endoscopist, such as lesions in a difficult area (lesser curvature of the stomach, duodenal angle) or in areas covered by blood/clots or incorrect assessment in less obvious lesions due to hypovolemia or intermittent bleeding (e.g. angiodysplasia) [51]. In the event of rebleeding after a negative endoscopy, re-endoscopy of the upper GI tract for a better assessment should be reevaluated before proceeding with a lower GI endoscopy, especially in patients with increased blood urea on admission [52].

Performing capsule enteroscopy within two days from the onset of bleeding results in a higher diagnostic yield, higher therapeutic intervention rate and shorter hospital stay [53]. Therefore, capsule enteroscopy application within the first 48 hours could improve the outcome of patients with overt obscure gastrointestinal bleeding [53].

Management of antithrombotic agents during acute bleeding.

Today, more and more patients presenting with ANVUGIB are taking aspirin and/or other antithrombotic drugs [54]. Antithrombotics should be interrupted while in some cases where bleeding occurs immediately after placement of coronary stents, continuation of these

drugs is vital and possibly in patients with non-severe self-limiting bleeding they should be continued with co-administration of high-dose PPIs and endoscopic hemostasis [55].

In cases of discontinuation of antithrombotic drugs, the question is (which is) the most appropriate time of reintroduction [56]. It has been shown that delayed re-initiation is associated with an increased incidence of fatal cardiovascular events, while rapid re-initiation is associated with an increased, but non-significant, risk of rebleeding [56]. Today, it is recommended to re-initiate aspirin on the 3rd-7th day, following successful endoscopic hemostasis, depending on the necessity of administration and the severity of the bleeding [54].

In patients taking vitamin K antagonists, who present with a bleeding event, fresh frozen plasma is preferred to vitamin K because of its immediate effect and the easiness to regain the previous level of anticoagulation once the bleeding stops [57]. However, fresh frozen plasma administration should not be routinely used, but could be considered for patients with a life-threatening gastrointestinal bleeding or a highly increased INR, substantially exceeding the therapeutic range [58]. Complete normalization of clotting times is not necessary to perform endoscopy. Endoscopy and endoscopic hemostasis, if needed, can be performed when prothrombin time drops to therapeutic levels [59].

Warfarin anticoagulants should be re-administered as soon as possible if there is a documented reason [60]. For as long as the patient does not receive oral anticoagulants and following cessation of bleeding, we administer heparin (intravenously or subcutaneously) which has a more direct and controlled anticoagulant effect and is easily reversible by stopping it [60].

Regarding the newer oral anticoagulant drugs, reversal agents can be administered in special cases, but due to the short half-life (12-18 hours), the limited evidence of benefit and the high cost, their administration is not recommended [61-62]. In severe cases of bleeding with dabigatran, hemodialysis may help, while it does not help in cases with apixaban and rivaroxaban which are more tightly bound to plasma proteins [61-62].

General preventive measures of patients with bleeding

After bleeding has stopped, the underlying disease should be treated to reduce the risk of bleeding recurrence [63]. Patients with ulcers should be tested for *Helicobacter pylori* infection and, if present, eradication therapy is mandatory [63]. Eradication of *Helicobacter pylori* leads to 75% lower risk of ulcer rebleeding compared to those under only continued antisecretory therapy [63]. Although *H. pylori* detection tests exhibit lower sensitivity during acute bleeding, testing and eradication regimens may be started as soon as possible, because delays in *H. pylori* eradication therapy are associated with time-dependent increase in the risk of recurrent ulcer and complications [64].

Based on our experience, patients should avoid NSAIDs in any form and if indicated COX-2 selective prostaglandin inhibitors may be an alternative solution, which do not have significant gastric toxicity. Before starting treatment with aspirin and/or NSAIDs in patients with a positive history of ulcer, an endoscopy should be performed to exclude the presence of ulcers. When aspirin or NSAIDs are necessary, co-administration with PPIs is mandatory. Also in older people, PPIs should be co-administered (in the standard dose) with NSAIDs or aspirin, which seems to prevent peptic ulcer disease and complications.

CONCLUSIONS

Upper gastrointestinal bleeding remains a common cause of hospital admissions worldwide. RCTs and meta-analyses confirm improved outcomes from a relatively restrictive approach to blood transfusion and a benefit from post-endoscopy high dose PPIs for high risk peptic ulcer bleeding. Endoscopic therapy has advanced dramatically today with recent additions, including hemostatic powder spray, over-the-scope clips and doppler probes, to join the established and widely used injection therapies, thermal probes, and clips. According to the above, a multidisciplinary collaboration is required to optimize outcomes of patients presenting with ANVUGIB.

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