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Malignant Hypertension: Current Perspectives and Challenges

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Malignant hypertension is a hypertensive emergency, with rapid disease progression and poor prognosis. Although recognized as a separate entity more than a century ago, significant knowledge gaps remain about its pathogenesis and treatment. This narrative review summarizes current viewpoints, research gaps, and challenges with a view to pooling future efforts at improving treatment and prognosis.

About 0.5% to 3% of all emergency department visits concern individuals who present with a suspected hypertensive emergency. One quarter of them have a hypertensive emergency that requires urgent treatment to lower blood pressure (BP) to safe levels.[1] Hypertensive emergencies are potentially life-threatening manifestations of hypertension, associated with acute impairment of ≥1 organs including the large arteries, heart, kidney, and brain.[2] The Studying the Treatment of Acute Hypertension registry reported 6.9% hospital mortality and a 37% readmission rate 90 days after discharge for a hypertensive emergency in 25 US institutions, between January 2007 and April 2008.[3] Of the different types of hypertensive emergencies, malignant hypertension (MHT) is characterized by extreme BP elevations and acute microvascular damage affecting various organs, in particular the retina, brain, and kidney (Table).[2,4–7] Data on prevalence and incidence of MHT are sparse. In large multi-ethnic urban communities in Birmingham (United Kingdom) and Amsterdam (Netherlands), overall incident rates of MHT have been 2 new cases per 100 000 individuals per year, with up to 4-fold higher rates (7.3 per 100 000 per year) reported for self-reported Black-African/Afro-Caribbean ethnicity.[8] While survival after MHT has considerably improved, it is still associated with significant morbidity and mortality. Amraoui et al reported an all-cause mortality of 10% at 5 years in patients with a mean age of 44 years,[9] while 20% needed a kidney replacement. Yet MHT has received little attention from the medical and scientific community, and diagnostic and therapeutic guidelines are mainly based on consensus rather than robust data, while definitions are not uniform (Table).[2]

In this review, we summarize current viewpoints on MHT, highlight ongoing challenges in its management, and propose future investigations to improve patient care.

EPIDEMIOLOGICAL CHALLENGES

While progress in the treatment and control of hypertension in the population at large has resulted in a decline in the number of MHT cases, it still exists. Recent evidence from the Birmingham, Bordeaux[10] and Amsterdam MHT registries suggests that the number of cases is rising,[2,8] in particular among ethnic minority groups. In the Bordeaux cohort, mean inclusions increased from 3 to 5 patients per year between 2001 and 2006 to >15 after 2016. In line with this observation,

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Table 1. Agreement and Disagreement About Malignant Hypertension Definition in Latest Hypertension Guidelines/ Consensus

Guidelines/DOI	Definition	Agreement and disagreement
ISH 2020[4]	Severe blood pressure elevation (commonly >200/120 mm Hg) associated with advanced bilateral retinopathy (hemorrhages, cotton wool spots, papilledema)	Need for severe rise in blood pressure is commonly accepted, but no specific threshold has been validated to date. In this context, presence of severe hypertensive retinopathy triggers diagnosis of malignant hypertension. This is a consensus. Whether it is mandatory in presence of heart, kidney, brain damage, and/or thrombotic microangiopathy is debated, as is need for bilateral retinal involvement or presence of papilledema. Isolated dry exudates, cotton wool spots, and hemorrhages may also evoke severe hypertensive retinopathy
NICE 2019[5]	Severe increase in blood pressure to 180/120 mm Hg or higher (and often >220/120 mm Hg) with signs of retinal hemorrhage and/or papilledema (swelling of optic nerve). Usually associated with new or progressive target organ damage	Committee agreed that further research is needed in this area. No relevant clinical studies or published evidence were identified during review process
ESC/ESH 2018[6]	Malignant hypertension is a hypertensive emergency characterized by presence of severe BP elevation (usually >200/120 mm Hg) and advanced retinopathy, defined as bilateral presence of flame-shaped hemorrhages, cotton wool spots, or papilledema	Authors stated that rate and magnitude of BP increase may be at least as important as absolute BP level in determining magnitude of organ injury
European Consensus 2018[2]	Coexistence of high BP values (often >200/120 mm Hg) with advanced retinopathy (defined as bilateral presence of flame-shaped hemorrhages, cotton wool spots, or papilledema), acute renal failure, and/or thrombotic microangiopathy. Because systemic microcirculatory damage is a pathological hallmark of malignant hypertension, and retinal lesions can be absent in patients with acute microvascular damage to kidney and brain, acute hypertensive microangiopathy could be an alternative term	Plea for broader definition, considering gaps in evidence and pathophysiology of disease, because retinal lesions may be absent in patients with acute microvascular damage to kidney, heart, and brain
AHA 2017[7]	Not mentioned	Malignant hypertension not mentioned in section on hypertensive emergencies, reflecting oversight of this form by medical community

BP indicates blood pressure.

the number of patients on hemodialysis owing to MHT has also increased in hemodialysis registries in the Netherlands and elsewhere in Europe. MHT is probably underdiagnosed, being classified as hypertensive emergency or being missed for several reasons: (1) BP may not be taken initially because patients often present with atypical symptoms, including headache, visual disturbances, or gastrointestinal complaints; (2) differentiating between severe uncontrolled hypertension and malignant hypertension maybe challenging if target organs are not systematically screened[11]; (3) the clinical presentation is heterogeneous with cardiac, renal, or neurological forms sometimes predominating and involving several disciplines.[10]

In summary, the main challenge from the clinical epidemiology point of view is to define the current incidence and prevalence of malignant hypertension in developing countries and to specify the characteristics of patients and different care pathways involved (Figure). This may help increase awareness about the disease among physicians managing MHT. A prospective international registry should be set up to answer these questions.

CLINICAL RESEARCH CHALLENGES

To improve the management of patients with MHT, clinical research must be strengthened. Currently, diagnostic criteria and treatment proposals can only be based on consensus, as no solid scientific evidence is available in this area.

Clinical Diagnosis

There is debate whether the traditional definition fully captures the extent of the microvascular damage associated with MHT and whether a more extensive definition should be used to better identify patients with acute microvascular damage. This is also reflected in current definitions which, to various degrees, tend to go beyond the original definition (see Table). A recent proposal is based on the presence of multiorgan

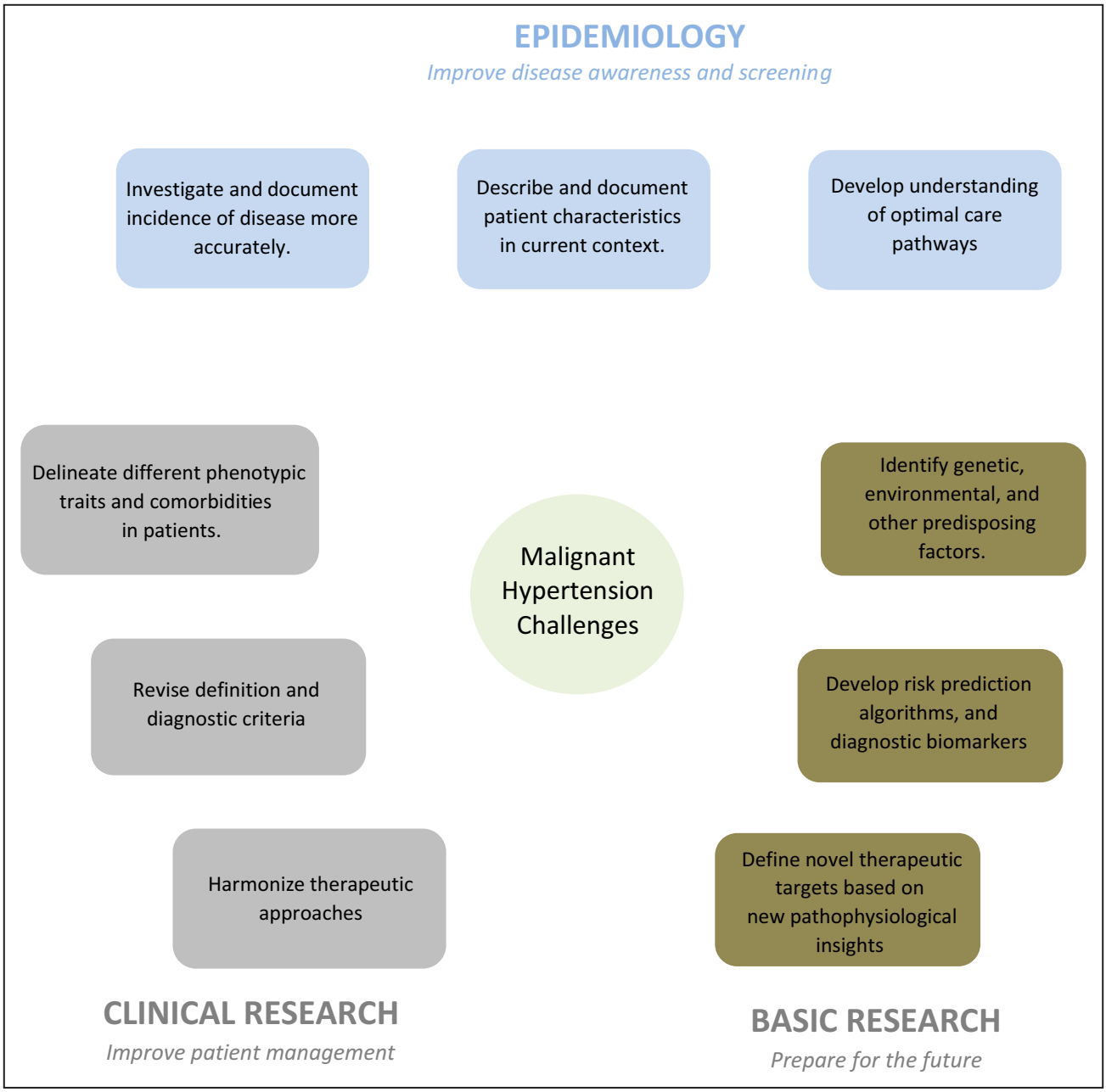

Figure. **Challenges in malignant hypertension research and management.**

damage to define MHT, even if the fundus is normal or data are not available.[12] This definition assumes the availability of modern diagnostic methods to explore target organ damage resulting from microcirculatory damage, including blood and urine samples for the evaluation of thrombotic microangiopathy and acute kidney injury, respectively, and cerebral and cardiac magnetic resonance imaging.[12] Future research is needed to establish whether patients with the classical or the new definition share the same prognosis and clinical and paraclinical features.

Challenges With Heterogeneous Presentations and Associated Factors

It is widely considered that any condition that results in a significant BP increase (such as associated kidney disease or renal artery stenosis, use of pressor or toxic agent, poor adherence) may further worsen BP control in those who are untreated or uncontrolled despite medication and present them with signs and symptoms consistent with MHT.[2] Pregnancy is another known precipitating factors.

To what extent genotype and pathophysiological background differ between such patients remains elusive, and whether understanding of these differences would improve their management or lead to new therapeutic pathways is still a matter of conjecture. In the Bordeaux cohort, most common reasons for hospital admission were visual impairment (25%), stroke (21%), and heart failure (10%), while the remaining patients were admitted for high BP (20%) and less specific symptoms including headaches, dizziness, anorexia, and asthenia (17%).[10] Although the original article in 1928 described the cardiac, neurological, and renal forms of the disease,[13] it is still unclear why these organs are particularly affected, even though autopsy studies reported generalized microvascular damage.[14]

Limited Therapeutic Options

The optimal treatment for MHT remains to be established. Traditional intravenous therapy reducing mean BP of 25% in the first hours is being challenged in uncomplicated MHT. Inappropriate management may cause microvascular damage and result in irreversible tissue injury, while vigorous BP-lowering treatment has resulted in ischemic stroke and death. Research has shown that cerebral autoregulation is impaired in patients with MHT, making them prone to cerebral hypoperfusion when BP is lowered. Whether intravenous therapy is always necessary is a matter of debate given recent reports that oral medication can also result in the controlled reduction of BP.[2,15] To date, no specific study has been conducted to answer these questions.

In summary, the main clinical challenges are as follows: (1) to better understand the different phenotypic presentations of MHT, and how their identification could improve patient management; (2) to update the definition and diagnostic criteria of MHT and to improve our therapeutic knowledge of it; and (3) to standardize and simplify the guidelines in terms of administration route, drug type, and BP targets (Figure).

BASIC SCIENCE CHALLENGES

The reason why some patients progress to MHT and others do not remains an enigma. In historical cohorts of patients with untreated hypertension, only 6% to 8% progress to MHT.[16] Progression to MHT likely results from a complex interaction of genetic and environmental factors. Past evidence points to the key role of the renal and renin-angiotensin system in both animal models and in humans.[17,18] However, polymorphisms in the complement system may also predispose patients to thrombotic microangiopathy and MHT,[19] while the involvement of other relevant pathways involving the profibrotic and antiangiogenic systems remains unexplored.

In summary, the basic science challenges are to identify new pathophysiological pathways that could help define specific biomarkers for the risk assessment, diagnosis, and monitoring of MHT. This could lead to targeted prevention strategies involving personalized medicine and new therapeutic approaches based on specific pathophysiological data (Figure).

CONCLUSIONS

The management of MHT is mainly based on consensus gleaned from clinical expertise and evidence of inadequate quality. Accumulating good-quality data through multicenter registries, comparative trials, and centralized biobanks could help improve the assessment and management of these patients. In this perspective, the Hypertension Arterielle MAligne (HAMA) project (NCT03755726) aims to become an international prospective database that would create a powerful platform for collaborative research on MHT.

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