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Managing Multimorbidity in Clinical Practice: Cross-Disciplinary Case Insights and Mechanistic Perspectives

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Abstract

In an era of advancing medical specialization, the concept of disease as an isolated entity is increasingly obsolete. Multimorbidity—the coexistence of multiple chronic conditions—has become the norm, particularly in aging populations. Within this broader framework, a specific subset of interactions, termed "Reciprocal Complications," presents distinct challenges to global health systems. These conditions involve diseases that mutually exacerbate one another, creating a vicious cycle that defies traditional, unidirectional models of comorbidity. Despite the complexity of these interactions, clinical management often remains fragmented and discipline-specific. Drawing on emerging evidence, this article calls for a paradigmatic shift in how we conceptualize, investigate, and manage such bidirectional disease relationships.

Introduction

Understanding Multimorbidity—Reciprocal Complications

Reciprocal complications refer to bidirectional disease interactions, wherein the presence or progression of one condition aggravates another. Unlike traditional comorbidity (the coexistence of conditions without direct causal links) or unidirectional complications (e.g., diabetes leading to retinopathy), these conditions reinforce each other through self-perpetuating feedback loops. Representative examples include:

- **Heart Failure (HF) and Chronic Kidney Disease (CKD):** HF exacerbates CKD by reducing renal perfusion, while CKD worsens HF through mechanisms such as fluid overload. This "two-way traffic" of harm presents a challenge to conventional management approaches based on linear disease models **[1,2].**
- **Cardiovascular Disease (CVD) and cancer**: The emerging disciplines of oncocardiology and reverse oncocardiology reveal how CVD and cancer—two leading global causes of death—interact pathophysiologically. Approximately 30% to 50% of cancer patients also have heart disease, and nearly 50% of patients with CVD have pre-existing or concurrent cancer **[3-6].**
- **CVD and liver diseases**: The fields of hepatocardiology or cardio-hepatology explore similar bidirectional interactions, where liver dysfunction affects cardiac health and vice versa **[7,8].**
- **Other examples** include Atrial Fibrillation (AF) and stroke **[9,10],** AF and HF **[11,12],** and HF and osteoporosis **[13,14].** These interrelated conditions not only amplify disease severity and accelerate functional decline but also increase mortality beyond the additive risk of individual diseases.

A hallmark of Reciprocal Complications is their self-sustaining nature, often driven by shared pathophysiological mechanisms, organ crosstalk, and treatment-induced adverse effects **[15-19].** At the molecular level, the "interactome"—a dynamic network of interconnected disease pathways—sustains these vicious cycles, underscoring the urgent need for mechanism-based, targeted therapeutic interventions **[20,21].**

Case Series

Multimorbidity Management Case Presentation

Case 1: Diabetes mellitus with cardiovascular disease and chronic kidney disease

Case summary

A 65-year-old male with a 10-year history of type 2 diabetes presented with chest pain and peripheral edema. He was diagnosed with diabetic nephropathy (renal insufficiency), coronary artery disease (three-vessel involvement), and hypertension. Management required a careful balance of glycemic control, renal protection, and cardiac care. The therapeutic approach—comprising insulin, an Angiotensin Receptor Blocker (ARB), and interventional surgery—resulted in significant clinical improvement.

Holistic targeting of shared pathways

- SGLT2 inhibitors (e.g., dapagliflozin) lower blood glucose and blood pressure while reducing cardiovascular and renal events by promoting urinary glucose excretion and enhancing endothelial function.
- Angiotensin Receptor Blockers (ARBs) offer renal protection and mitigate cardiac remodeling, targeting dual-organ damage.

- Balancing trade-offs: Avoidance of nephrotoxic agents (e.g., metformin in advanced kidney disease) is essential. Therapeutic choices should prioritize agents with demonstrated multi-organ benefits.

Case 2: Lung adenocarcinoma with interstitial lung disease and immune pneumonitis

Case summary

A 70-year-old female with lung adenocarcinoma harboring an EGFR mutation and pre-existing interstitial lung disease (idiopathic pulmonary fibrosis, IPF) developed severe immune-related pneumonitis following PD-1 inhibitor therapy, leading to respiratory failure. She responded to a combination of glucocorticoids and antifibrotic therapy, and her cancer treatment was subsequently switched to targeted therapy with osimertinib.

Risk stratification and personalization

- Avoiding over generalized contraindications: Rather than a blanket exclusion of immunotherapy in ILD, clinicians should assess baseline lung function (e.g., FVC, DLCO) and tumor aggressiveness to individualize treatment.
- Targeted therapy transition: Switching to osimertinib in EGFR-mutant tumors minimized immune toxicity while directly inhibiting oncogenic signaling.
- Dual-focus treatment: Glucocorticoids reduced immune-mediated lung injury, while antifibrotics (e.g., nintedanib) addressed the underlying fibrotic process, leveraging shared anti-inflammatory mechanisms.

Case 3: Major depression with irritable bowel syndrome and obesity

Case summary

A 35-year-old female with longstanding major depressive disorder presented with recurrent abdominal pain and diarrhea consistent with Irritable Bowel Syndrome (IBS), along with a BMI of 28.5. Following a multimodal approach involving Cognitive Behavioral Therapy (CBT), probiotics, and a low-FODMAP diet, her depression score decreased by 50%, abdominal pain episodes were reduced by 70%, and she experienced a 4 kg weight loss.

Interdisciplinary mechanism targeting

- Gut microbiota modulation: Probiotics and a low-FODMAP diet helped restore a healthy microbiome, reduce intestinal inflammation, and improve mood through gut–brain axis modulation via the vagus nerve.
- Psychological intervention: CBT disrupted the "stress–IBS–depression" cycle by reshaping maladaptive cognitive responses to gastrointestinal symptoms.
- Lifestyle synergy: Weight loss achieved through dietary changes and physical activity reduced systemic inflammation and enhanced both metabolic and psychological well-being, addressing the triad of conditions concurrently.

Core Values of Multimorbidity Case Reports

- ✓ **Revealing complex pathophysiological associations**

Multimorbidity case reports help elucidate intricate disease networks—for example, how metabolic dysregulation can initiate vascular injury, ultimately triggering cascades of multi-organ dysfunction. These cases shed light on the interconnected nature of disease progression.

- ✓ **Optimizing diagnostic and therapeutic decisions**

Real-world cases validate the importance of Multidisciplinary Teamwork (MDT) and the application of polypharmacological strategies. By targeting multiple critical disease factors or pathways—through combinational pharmacotherapy or multitarget agents—clinicians can move beyond "isolated organ" treatment models to achieve more comprehensive care **[22,23].**

- ✓ **Driving guideline development and therapeutic innovation**

Case-based evidence supports the creation of integrated clinical guidelines across disease categories and encourages the development of novel therapeutic approaches, including multi-target inhibitors and rational drug combinations.

- ✓ **Enhancing clinician and patient awareness**

Multimorbidity reports reinforce the need for clinicians to view patients holistically, focusing on overall health rather than individual conditions. They also encourage patients to recognize and proactively manage coexisting diseases.

Transitioning from siloed disease management to a model that recognizes and addresses the interconnected nature of health conditions has far-reaching implications for clinical practice, biomedical research, and healthcare policy. Embracing this paradigm shift will foster more effective therapeutic strategies and deepen our understanding of emerging clinical complexities. Ultimately, the future of medicine lies in integrated, systems-based approaches that improve both outcomes and quality of life for patients living with multiple chronic conditions.

References

1. Beldhuis IE, Lam CSP, Testani JM, Voors AA, Van Spall HGC, Ter Maaten JM, et al. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. Circulation. 2022;145(9):693–712.
2. Matsushita K, Ballew SH, Wang AY, Kalyesubula R, Schaeffner E, Agarwal R. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol. 2022;18(11):696–707.
3. Aboumsallem JP, Moslehi J, and de Boer RA. Reverse cardio-oncology:Cancerdevelopmentin patients with cardiovascular disease. J Am Heart Assoc. 2020;9(2):e013754.
4. Moslehi J, Fujiwara K, Guzik T. Cardio-oncology: a novel platform for basic and translational cardiovascular investigation driven by clinical need. Cardiovasc Res. 2019;115:819–823.
5. Al-Kindi, SG, Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: The unmet need for onco-cardiology. Mayo Clin Proc. 2016;91(1):81–83.
6. de Boer RA, Meijers WC, van der Meer P, van Veldhuisen DJ. Cancer and heart disease: associations and relations. Eur J Heart Fail.2019;21(12):1515–1525.
7. CazacGD, Lăcătușu CM, Mihai C, Grigorescu ED, Onofriescu A, Mihai BM. New insights into non-alcoholic fatty liver disease and coronary artery disease: The liver-heart axis. Life (Basel). 2022;12(8):1189.
8. Taniguchi T, Lee SS. Cardio-Hepatology: Connections Between Hepatic and

Cardiovascular Disease. Academic Press (London, United Kingdom). 2023; ISBN: 978-0-12-817394-7.

9. Bernstein RA,Kamel H, Granger CB, Piccini JP, Katz JM, Sethi PP, et al. STROKE AF Investigators. A trial fibrillation in patients with stroke attributed to large- or small-vessel disease: 3-Year results from the STROKE AF randomized clinical trial. JAMA Neurol. 2023;80(12):1277–1283.
10. Kamel H. Reassessing the implications of a trial fibrillation detected after stroke. Lancet Neurol. 2024;23(1):9–11.
11. Khazanie P, Liang L, Qualls LG, Curtis LH, Fonarow GC, Hammill BG, et al. Outcomes of medicare beneficiaries with heart failure and a trial fibrillation. JACC Heart Fail. 2014;2(1):41–48.
12. Ebbesen MN, D'Souza M, Andersson C, Butt JH, Madelaire C, Biering-Sorensen T, et al. Rate of heart failure following a trial fibrillation according to presence of family history of dilated cardiomyopathy or heart failure: A nationwide study. J Am Heart Assoc. 2021;10(22):e021286.
13. van Diepen S, Majumdar SR, Bakal JA, McAlister FA, Ezekowitz JA. Heart failure is a risk factor for orthopedic fracture: a population-based analysis of 16,294 patients. Circulation. 2008;118(19):1946–1952.
14. Ge G, Li J, Wang Q. Heart failure and fracture risk: a meta-analysis. Osteoporos Int. 2019;30(10):1903–1909.
15. Costanzo V,Ratre YK, Andretta E,Acharya R, Bhaskar LVKS, Verma HK. A Comprehensive Review of Cancer Drug–Induced Cardiotoxicity in Blood Cancer Patients: Current Perspectives and Therapeutic Strategies. Curr Treatment Options Oncol. 2024;25:465–495.
16. Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. Nat Rev Endocrinol.2024;20(1):27–49.
17. Matsuura R, Doi K, Rabb H. Acute kidney injury and distant organ dysfunction-network system analysis. Kidney Int. 2023;103(6):1041–1055.
18. Yuan W, Song C. Crosstalk between bone and otherorgans. Med Rev. 2022;2(4):331–348.
19. Oishi Y, Manabe I.Organsystemcrosstalkin cardiometabolic disease in the age of multimorbidity. Front Cardiovasc Med. 2020;7:64.
20. Menche J, Sharma A, Kitsak M, Ghiassian SD, Vidal M, Loscalzo J. et al. Disease networks. Uncovering disease-disease relationships through the incomplete interactome. Science. 2015;347(6224):1257601.
21. Yang X, Xu W, Leng D, Wen Y, Wu L, Li R, et al. Exploring novel disease-disease associations based on multi-view fusion network. Comput Struct Biotechnol J. 2023;21:1807-1819.
22. Wang Z, Yang B. Polypharmacology: Principles and Methodologies. Volume I& II. Springer Nature (Switzerland AG), Gewerbesrasse 11, 6330 Cham, Switzerland. 2022. ISBN-13: 978-3-031-04997-2/eISBN: 978-3-031-04998-9.
23. Wang Z. Anti-Aging Polypharmacology. Cambridge Scholars Publishing (UK), 2024.

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