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"Understanding the Evolving Landscape of Influenza Antiviral Resistance"

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SUMMARY:

Influenza imposes a substantial burden on society and healthcare systems. While antiviral medications are a critical component of effective influenza management, the potential for the emergence of antiviral-resistant viral strains can lead to uncertainty and hesitation among frontline prescribers and policymakers. This paper provides an overview of influenza antiviral resistance, exploring the key concepts underlying its development and clinical impact. Given the acute nature of influenza in immunocompetent patients, although available data are limited by small numbers of cases, they suggest that antiviral treatment still provides clinical benefit to the patient in whom resistance emerges. Importantly, however, resistant viruses are often associated with reduced fitness, such that their widespread transmission is relatively rare. This overview aims to inform decision-making and optimize the use of influenza antivirals in the face of the potential emergence of resistant strains.

INTRODUCTION:

- Influenza poses a significant global health burden, with approximately 1 billion annual infections, millions of hospitalizations, and up to 600,000 excess deaths.
- This burden persists despite available vaccines and antivirals, and is exacerbated by the ongoing impact of the COVID-19 pandemic.
- While vaccination is the preferred prevention method, it has limitations including variable efficacy, strain mismatches, long production timelines, and within-season waning of effectiveness.
- Antivirals are therefore critical for the management and control of influenza, by directly targeting the virus and reducing morbidity and mortality.
- Clinical trials and real-world data demonstrate that antivirals are a critical tool for managing influenza.
- reluctance to utilize antivirals may contribute to the substantial morbidity and mortality burden of influenza.
- To address these concerns, this overview explores the underlying concepts of antiviral resistance in influenza, drawing parallels to antibiotic resistance in bacteria.

THE EVOLUTION OF DRUG RESISTANCE

Natural Selection and Viral Mutations

- Influenza viruses, like most RNA viruses, are subject to rapid mutation and replication, generating a diverse viral population within each infection.
- While most mutations are detrimental, some can confer advantageous traits like antiviral resistance.
- When a resistant viral variant emerges during drug exposure, it has a selective advantage, allowing it to proliferate more than drug-sensitive strains.

Patterns of Resistance

- Antiviral resistance has been observed for all known influenza treatments.
- Resistance can emerge rapidly within individual patients.
- Resistance rates can vary between influenza virus types and subtypes, with lower rates typically seen for influenza B compared to A viruses.
- Factors like differential antiviral inhibition and viral fitness may contribute to these subtype-specific differences in resistance.

The Implications

- The evolution of antiviral resistance poses a significant challenge for influenza management and control.
- Understanding the underlying mechanisms is crucial to mitigate the risks and impact of resistant strains on patient outcomes and public health.

Influenza Antiviral	Mechanism of Action	Administration Route	Standard Adult Treatment Regimen	Year of First Approval	Patient Populations with Demonstrated Efficacy from RCT Data
1. **Amantadine**	M2 ion channel inhibitor	Oral	Once daily for ≤10 days (U.S.)	1966	Otherwise healthy (72), prophylaxis (73)
2. **Rimantadine**	M2 ion channel inhibitor	Oral	Twice daily for 7 days	1993	Otherwise healthy (74), children (75), prophylaxis (73)
3. **Zanamivir**	Neuraminidase inhibitor	Inhalation or intravenous	Twice daily for 5 days (inhalation) or twice-daily infusion for 5–10	1999	Otherwise healthy (76), children ≥5 yrs of age (77), prophylaxis (78, 79)

				days (intravenous)		
4.	**Oseltamivir**	Neuraminidase inhibitor	Oral	Twice daily for 5 days	1999	Otherwise healthy (78, 80), high risk of complications (53), children ≥1 yr of age (51), prophylaxis (81)
5.	**Peramivir**	Neuraminidase inhibitor	Intravenous	Single infusion over 15 min (minimum)	2014	Otherwise healthy (82)
6.	**Laninamivir**	Neuraminidase inhibitor	Inhalation	Single dose	2010	Otherwise healthy (83), children (≤9 yrs of age) (84), prophylaxis (85)
7.	**Baloxavir**	Endonuclease inhibitor	Oral	Single dose	2018	Otherwise healthy (49), high risk of complications (53), children ≥1 yr of age (54), prophylaxis (86)
8.	**Favipiravir**	RNA-dependent RNA polymerase inhibitor	Oral	Twice daily for 5 days	2014	Otherwise healthy (87)
9.	**Arbidol**	Hemagglutinin inhibitor	Oral	Three times daily for 5-7 days	2005	Otherwise healthy (88), high risk of complications (89), children ≥6 yrs of age (90)
10.	**Umifenovir**	Hemagglutinin inhibitor	Oral	Three times daily for 5-7 days	1993	Otherwise healthy (91), high risk of complications (92), children ≥6 yrs of age (93)
11.	**Inavir**	Neuraminidase inhibitor	Inhalation	Single dose	2010	Otherwise healthy (94), children ≥5 yrs of age (95), prophylaxis (96)

Summary of widely approved influenza antivirals

Mechanisms of Resistance

Influenza viruses can develop resistance to antiviral drugs through specific amino acid changes in their proteins. These changes alter the structure and function of the viral proteins, reducing the effectiveness of the drugs.

For the M2 inhibitors (adamantanes), the most common resistance mutation is S31N, which disrupts the drug's binding to the M2 protein. This mutation is now found in almost all circulating influenza A viruses, rendering the adamantanes ineffective.

For the neuraminidase inhibitors (NAIs), different amino acid substitutions in the neuraminidase enzyme can affect the binding of specific NAIs. For example, H275Y in H1N1 viruses reduces susceptibility to oseltamivir and peramivir, but not to zanamivir or laninamivir.

The endonuclease inhibitor baloxavir has also seen the emergence of the I38T resistance mutation, primarily in H3N2 viruses. This mutation reduces the drug's interaction with the viral polymerase complex.

While resistance rates to NAIs and baloxavir remain low (less than 1% and 0.1%, respectively), resistance to the adamantanes is effectively 100%. This highlights the importance of developing new antiviral drugs with different mechanisms of action, to ensure alternative treatment options if resistance develops.

Ongoing research is focused on novel M2 inhibitors and polymerase inhibitors, such as pimodivir and favipiravir, to address the resistance issue. However, some of these new drugs have encountered challenges in clinical trials.

Antiviral Resistance vs. Antibiotic Resistance

The global crisis of antimicrobial resistance has prompted widespread awareness campaigns targeting healthcare providers. However, a crucial distinction is often overlooked - the fundamental differences between antibiotic resistance and influenza antiviral resistance, and their respective implications.

Antibiotic resistance poses a grave concern, as the indiscriminate use of these drugs can lead to the development of permanent, widespread resistance in commensal bacteria within the human body. This can have significant detrimental effects on the host.

In stark contrast, influenza infections are acute, with the virus being fully cleared within 1-3 weeks in immunocompetent individuals. This rapid clearance means that the use of influenza antivirals in misdiagnosed patients will not contribute to resistance emergence. Furthermore, even if a resistant viral variant arises during an acute infection, the immune system will effectively clear the infection, without impacting the management of future influenza cases - provided drug-sensitive strains remain predominant globally.

Another crucial difference lies in the spectrum of activity. Antibiotics are often broad-spectrum, potentially promoting resistance in both targeted pathogens and commensal bacteria. Conversely, influenza antivirals are engineered to be highly specific, targeting conserved regions exclusive to influenza viruses, with no activity against non-influenza viruses.

Given these fundamental distinctions, clinicians must approach antibiotic and influenza antiviral therapies with tailored considerations, rather than applying a one-size-fits-all approach to anti-infective management. Recognizing the unique characteristics of antibiotic versus antiviral resistance is essential for developing appropriate, context-specific treatment strategies.

CLINICAL IMPACT OF ANTIVIRAL RESISTANCE

Implications of Antiviral Resistance in Acute and Chronic Viral Infections

In chronic viral infections, the host immune response is unable to clear the virus even with effective antiviral treatment. Therefore, if antiviral resistance develops, the clinical benefit is lost, and the resistant virus can persist in the population even if treatment is stopped. This limits the future utility of that antiviral or class of antivirals for that patient.

However, these concerns do not apply to acute infections like influenza, where viruses (resistant or sensitive) are cleared within a few weeks in most immunocompetent patients. In some immunocompromised patients, the likelihood of influenza antiviral resistance developing is greater due to prolonged viral shedding and extended antiviral treatment. This risk may be reduced with combination therapy using antivirals with different mechanisms of action.

Distinguishing Treatment-Emergent and Acquired Antiviral Resistance

It is important to distinguish between "treatment-emergent" resistance that arises during antiviral treatment of a single patient, and "acquired" resistance in a circulating virus that already has antiviral resistance when infecting a new host.

Rates of acquired resistance are often lower than treatment-emergent resistance, as evolving antiviral resistance normally imposes a fitness cost on the virus, preventing widespread transmission. However, there are exceptions where resistant viruses remain fit and transmissible.

The detection of treatment-emergent resistance provides no indication of the long-term fitness and transmissibility of the resistant virus, whereas the detection of high levels of acquired resistance implies that resistant viruses are able to efficiently transmit within a population

Characterizing the Clinical Implications of Antiviral Resistance

From the perspective of the healthcare provider and the patient, it is crucial to understand the clinical implications of antiviral resistance in viral infections. When it occurs, treatment-emergent resistance typically develops within the first few days of infection. This can result in a temporary increase in viral levels, particularly in young children, although the replication levels are significantly lower than earlier in the infection and may only last for 1-2 days before the immune system clears the virus.

While large-scale clinical studies have been conducted, drawing reliable conclusions on the clinical impact of treatment-emergent resistance is often challenging, as this occurs in a relatively small number of patients. Recent studies on the polymerase inhibitor baloxavir have shown mixed results, with one study indicating a 12-hour increase in symptom duration and another study suggesting an 11-hour shorter duration of symptoms in patients with treatment-emergent resistance. Importantly, even in the study where an extension of symptom duration was observed, patients with resistant viruses still retained substantial clinical benefit compared to those who received placebo.

Similarly, in pediatric studies, treatment-emergent resistance has been associated with slightly longer time to illness alleviation and fever resolution, but the overall clinical benefit of the antiviral treatment was maintained. Real-world surveillance data has also shown that while treatment-emergent resistance can have a minor effect on the clearance of residual virus, it does not impact symptom duration or resolution.

Importantly, there is no evidence that antiviral resistance would affect the safety profile of the respective influenza antivirals, and no published studies have reported an altered safety profile due to the development of resistance.

The Complex Dynamics of Resistant Influenza Viruses: Factors Governing Their Spread and Persistence

As noted previously, resistant viral variants often have a decreased ability to transmit between individuals and are therefore less fit compared to wild-type drug-sensitive viruses, all other factors being equal. This, coupled with the fact that resistance typically develops later in an infection and after any transmission event, provides a straightforward biological explanation for why acquired resistance is expected to be relatively uncommon. Additionally, as the virus transmits from one host to another, there is often a significant population bottleneck, with most new infections being initiated by a very small number of virions. As a result, any low-frequency resistance mutation could easily be lost from the population through random chance.

Despite this, even with reduced viral fitness, person-to-person transmission of resistant viruses can occur in confined settings such as households. Such short-lived, sporadic transmission has been documented for both oseltamivir- and baloxavir-resistant viruses.

However, the greater concern is the sustained interhost transmission of resistant viruses in the absence of drug treatment pressure, potentially leading to widespread global circulation. This phenomenon has been observed with both subtypes of seasonal influenza virus in humans, A/H1N1 and A/H3N2, where strains resistant to the M2 ion channel inhibitors (amantadine and rimantadine) emerged and remain in global circulation, rendering these drugs ineffective for influenza treatment.

Since 2009, there have been only a few reports of localized circulation of A/H1N1pdm09 oseltamivir-resistant viruses, and these have not become widespread. Similarly, there have been no reports of local clusters or widespread circulation of viruses resistant to other antivirals such as baloxavir or the neuraminidase inhibitors zanamivir and laninamivir.

Despite the relative rarity of these events, the ongoing potential for the global spread of resistance to front-line influenza antivirals is continuously monitored. It is important to note that the widespread circulation of resistance mutations cannot be attributed solely to greater antiviral usage. Factors such as the independent emergence of resistance mutations and the low frequency of resistant mutations even in the presence of high antiviral usage suggest that there are complex biological and evolutionary factors at play.

MONITORING RESISTANCE: UNDERSTANDING THE DYNAMICS OF ANTIVIRAL-RESISTANT VIRUSES

Assessing the Emergence of Treatment-Induced Resistance

Estimating the rates of treatment-emergent resistance, where patients develop resistant viral variants due to antiviral therapy, is typically based on data from clinical trials. This involves collecting paired patient samples - one before treatment and one after - and analyzing them to detect the presence of resistance-conferring mutations that arose during the course of treatment.

However, it is important to note that these resistance rate calculations can be influenced by the specific methodology used:

- Only patients with detectable virus after treatment (usually days 3-5) are included in the denominator, while those who clear the virus by the second sampling point are excluded. This can lead to an overestimation of the true resistance rate, as those who cleared the virus are unlikely to have developed resistant strains.

- More effective antiviral drugs can result in fewer samples with detectable virus post-treatment, further reducing the denominator and accentuating this potential bias.

Therefore, it is crucial to be aware of the different ways resistance rates can be calculated and reported - using only patients with paired samples versus the full denominator of all treated patients. It is also important to distinguish between pre-existing and treatment-emergent resistance when assessing overall resistance levels in a population.

Key Points:

- Resistance rates are typically estimated from clinical trial data with paired pre- and post-treatment patient samples

- Methodological choices in the denominator can influence the reported resistance rates

- Exclusion of patients who clear the virus can lead to overestimation of treatment-emergent resistance

- Awareness of these factors is crucial for accurately interpreting and comparing resistance data

Understanding the Global Prevalence of Antiviral Resistance in Influenza Viruses

- The WHO Global Influenza Surveillance and Response System coordinates national organizations to monitor and assess the prevalence of antiviral resistance among circulating influenza strains.

- These resistance data are typically derived from viruses collected from untreated patients, providing an indication of the likelihood of encountering resistant strains in the community.

- To aid in making informed antiviral treatment choices, primary healthcare providers should stay up-to-date on the latest regional resistance rate updates provided by the WHO and other public health authorities.

Key Points:

- The WHO Global Influenza Surveillance System tracks antiviral resistance in circulating influenza strains.

- Resistance data are typically collected from untreated patients, reflecting community-level resistance.

- Recent global data showed low levels of resistance to key antiviral classes, indicating it is not a major concern for treatment.

- Healthcare providers should be aware of the latest regional resistance rate updates to guide their antiviral treatment decisions

Understanding the Role of Influenza Antivirals and Addressing Resistance Concerns

1. Influenza antivirals are crucial control measures for managing the illness, as they can shorten the duration and reduce the risk of complications and deaths, especially in high-risk and hospitalized patients.

2. Resistance to influenza antivirals is an expected outcome of the natural evolution of RNA viruses, similar to the case with SARS-CoV-2.

3. Unlike antibiotic-resistant bacteria, resistant influenza viruses are typically cleared from immunocompetent patients in a relatively short time and do not impact the future utility of the same antiviral if drug-sensitive strains remain dominant in the population.

4. The benefits of antiviral treatment for influenza, which affects up to 1 billion people and causes hundreds of thousands of deaths annually, outweigh the concerns about resistance.

5. Global and national influenza surveillance networks monitor the frequency of acquired resistance and provide this information to public health bodies to guide appropriate clinical management.

6. With the potential for long-term co-circulation of influenza and SARS-CoV-2, the complementary role of antivirals alongside vaccines in relieving the burden on healthcare systems should be acknowledged.

In conclusion, while the emergence of resistance is a reality, the overall benefits of influenza antivirals in managing the disease and its impact on public health justify their continued use, with appropriate monitoring and guidance from global health organizations.

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""فهم المشهد المتغير لمقاومة الفيروسات التاجية الأنفلونزا""

إعداد الباحثين:

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الملخص:

تفرض الإنفلونزا عبئًا كبيرًا على المجتمع وأنظمة الرعاية الصحية. بينما تُعتبر الأدوية المضادة للفيروسات عنصرًا حاسمًا في إدارة الإنفلونزا بشكل فعال، فإن احتمال ظهور سلالات فيروسية مقاومة للأدوية يمكن أن يؤدي إلى عدم اليقين والتردد بين الأطباء المعالجين وصانعي السياسات. تقدم هذه الورقة نظرة عامة على مقاومة الفيروسات للإنفلونزا، مستكشفة المفاهيم الرئيسية التي تكمن وراء تطورها وتأثيرها السريري. نظرًا للطبيعة الحادة للإنفلونزا لدى المرضى ذوي المناعة السليمة، على الرغم من أن البيانات المتاحة محدودة بسبب قلة عدد الحالات، إلا أنها تشير إلى أن العلاج المضاد للفيروسات لا يزال يوفر فائدة سريرية للمريض الذي تظهر لديه المقاومة. ومن المهم أن نلاحظ أن الفيروسات المقاومة غالبًا ما ترتبط بلياقة بدنية منخفضة، مما يجعل انتقالها على نطاق واسع نادرًا نسبيًا. تهدف هذه النظرة العامة إلى إبلاغ عملية اتخاذ القرار وتحسين استخدام الأدوية المضادة للفيروسات في مواجهة احتمال ظهور سلالات مقاومة.