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Neurosyphilis

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Neurosyphilis remains an important and highly morbid neurologic infection. Recent years have seen a dramatic increase in the incidence of syphilis across a variety of populations, making recognition of the many neurologic complications of this infection still relevant for modern clinicians. As manifestations of neurosyphilis are famously varied, a high index of suspicion is essential, especially in the face of atypical presentations. In this review, we discuss updates to the epidemiology, range of clinical presentations, diagnosis, and management of neurosyphilis.

ANN NEUROL 2025;00:1–7

Neurosyphilis is a clinical entity that has long fascinated and frustrated clinicians. Caused by invasion of the spirochete *Treponema pallidum* subspecies *pallidum* (hereafter referred to as *T. pallidum*) into the central nervous system (CNS), its manifestations can range from asymptomatic neuroinvasion to severe neurologic disability and parenchymal destruction. The historical importance of neurosyphilis in the evolution of contemporary medicine and neurology is difficult to ignore, as many elements of the modern neurologic examination trace their origins back to descriptions of patients with this infection.[1]

Yet, neurosyphilis is far from a disease of purely historical interest. Recent years have seen a dramatic increase in incidence of new syphilis infections in a variety of populations. Disturbingly, congenital syphilis cases are being described at the highest levels in 3 decades. Given this sustained increase in syphilis cases, neurologists need to be vigilant for new cases of neurosyphilis, as CNS involvement represents some of the most morbid manifestations of this disease.

Although much of what we know about neurosyphilis dates back to the pre-antibiotic era, recent years have seen several advances in our understanding of this condition. In this review, we will discuss the changing epidemiology of neurosyphilis, its range of clinical manifestations, an update on diagnostic approaches, and recommended treatments.

Epidemiology

Reported syphilis cases declined dramatically in the 1940s and 1950s following the expanded use of penicillin and remained low for several decades.[2] There was a slight increase in cases coinciding with the early human immunodeficiency virus (HIV) epidemic, although cases subsequently declined to an all-time low of 31,618 reported infections in the year 2000, with an annualized rate of 11.2 per 100,000 population.[2] Unfortunately, incident syphilis cases have steadily increased since (Fig A) 2001 with a sharp resurgence in the past decade and increases seen across several demographic groups. An estimated 209,253 cases were reported to the US Center for Disease Control and Prevention (CDC) in 2023, representing the highest number of cases since 1950.[2] Several disparities exist, with Black/African American and American Indian/Alaska Native individuals continuing to experience disproportionately high rates of primary and secondary (P&S) syphilis.[2] Roughly one-third of all reported P&S syphilis cases in 2023 occurred in men who have sex with men.[2] The rate of reported primary and secondary syphilis among women, although lower than that among men (8.1 vs 23.6 per 100,000), has also continued to rise sharply in recent years. Disturbingly, this increase in women aged 15 to 44 years has been accompanied by a parallel surge in cases of congenital syphilis (CS). In 2023, a staggering 3,882 CS cases (including 279 CS-related stillbirths and/or neonatal/infant deaths) were reported in the

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.78016

Received Apr 11, 2025, and in revised form Jun 24, 2025. Accepted for publication Aug 5, 2025.

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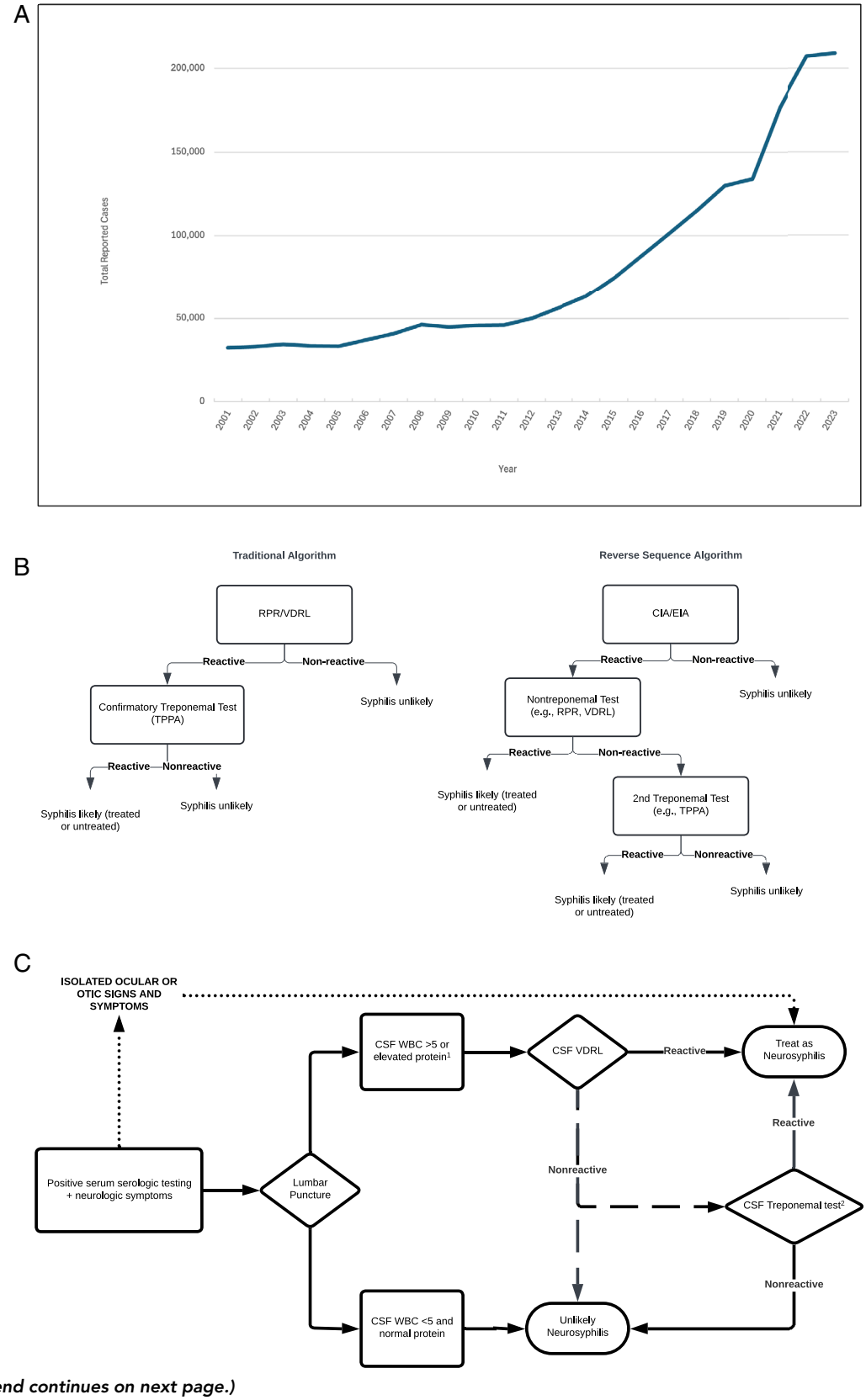

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United States, representing the largest number of CS cases since 1992 and a more than 10-fold increase compared with 2012 data.[2]

Although syphilis itself is a reportable disease, accurate tracking of neurosyphilis cases has represented something of a challenge for public health agencies. From 2009 to 2015, the proportion of early syphilis cases (primary, secondary, and early latent) reported to the CDC with identified neurosyphilis (confirmed via lumbar puncture [LP]) was estimated to be 1.8%, although this was suspected to be an underestimate of the true burden of disease.[3] Using manual case review, investigators from Washington State identified a rate of complicated syphilis (ie, those with neurologic, otic, or ocular involvement) among patients diagnosed with syphilis of any stage ranging from 3.5% to 7.9%, a figure higher than had been previously reported.[4]

Whereas the prior surveillance case definition required documentation of abnormal cerebrospinal fluid (CSF) results, the Council of State and Territorial Epidemiologists revised the syphilis case definition in 2018 to include additional information regarding the presence of neurologic, ocular, or otic symptoms in an effort to enhance reporting of complicated syphilis. Data from 2019 using the new case definition suggested a prevalence of neurologic, ocular, and otic symptoms of 1.1%, 1.1%, and 0.4%, respectively, among patients diagnosed with syphilis; this was still felt to be an incomplete snapshot of neurologic and ocular involvement of the infection, however.[5] Due to lack of clinical recognition and inconsistent reporting of neurologic complications of the disease, the true burden of neurosyphilis remains incompletely characterized but is presumed to be higher than published reports.

Clinical Manifestations

Neurosyphilis can occur at any stage of infection with *T. pallidum*, which has been demonstrated to invade the CNS even during the first few days of primary infection. The spectrum of neurosyphilis is broad and can include a range of atypical manifestations, making recognition and diagnosis particularly challenging. Neurosyphilis syndromes are traditionally classified as "early" (occurring within the first year after infection; eg, meningitis, and acute forms of ocular/otic syphilis) or "late" (occurring several years after infection; eg, general paresis, tabes dorsalis, and syphilitic amyotrophy), although concurrent infection with HIV may alter this timeline.

Asymptomatic neurosyphilis is defined by the presence of CSF abnormalities due to CNS invasion by *T. pallidum* in the absence of neurologic symptoms. In a case series of 748 patients from the pre-antibiotic era who did not exhibit neurologic symptoms, CSF abnormalities were present in 9.2% of seronegative primary infections, 23.4% of seropositive primary infections, and 20.2% of early secondary infections.[6] Similarly, a more contemporary study of patients with newly diagnosed syphilis who underwent LP demonstrated the presence of *T. pallidum* in the CSF of 30% (12/40) of participants, suggesting a high rate of early and frequently asymptomatic CNS invasion.[7]

Most cases of early symptomatic neurosyphilis present as meningitis, which classically arises within the first year after initial infection.[8–10] Symptoms commonly include headache, photophobia, nausea/vomiting, confusion, seizures, or symptoms related to various cranial nerve palsies.[8] Otic and ocular involvement may also be present in early infection. Otosyphilis typically presents with hearing loss, tinnitus, and/or dizziness, and can involve the cochleovestibular apparatus, the eighth cranial nerve, or the temporal bone itself (reflecting osteitis).[11] Common presentations of ocular syphilis include posterior or panuveitis, neuroretinitis, and optic neuritis, although any ocular structure can be involved.[12] Both otic and ocular syphilis can present with or without concurrent meningitis, and the absence of a CSF pleocytosis does not exclude either diagnosis.

FIGURE: (A) Increase in syphilis cases since 2001. Data from the United States Center for Disease Control and Prevention. Reported cases of syphilis in the United States have increased every year since 2001, rising sharply during the past decade, and with levels in 2023 representing the highest number of infections reported since 1950.[2] (B) Serum serology testing algorithms. The traditional algorithm starts with a quantitative nontreponemal test which rises and falls in response to disease activity. Due to the poor specificity of nontreponemal tests, however, a reactive test must be confirmed by a treponemal test (which is more specific but remains positive for life after infection). The reverse algorithm starts instead with a high throughput treponemal test (CIA/EIA); if positive, either current or prior infection is suggested and this algorithm reflexes to a quantitative nontreponemal test, which assess for disease activity. If negative, a confirmatory manual treponemal test (eg, TPPA) is performed. (C) CSF testing algorithm. In cases of suspected neurosyphilis (positive serum testing and neurologic symptoms), CSF testing should be performed. Inflammatory CSF (elevated WBC and/or protein concentration) should prompt sending a CSF VDRL serology. This is specific but imperfectly sensitive for the diagnosis of neurosyphilis. If clinical suspicion persists in the setting of a negative CSF VDRL, a negative CSF treponemal test could be used to exclude to exclude neurosyphilis based on its high negative predictive value. [1]Isolated elevations in protein are felt to be less specific for the diagnosis of neurosyphilis; [2]If clinical suspicion for neurosyphilis persists, including in complex cases with non-specific neurologic presentations, a CSF treponemal test may be utilized to help exclude neurosyphilis based on its high negative predictive value. CIA/EIA = chemiluminescent immunoassay/enzyme immunoassay; CSF = cerebrospinal fluid; TPPA = treponema pallidum particle agglutination; VDRL = venereal disease research laboratory; WBC = white blood cell.

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Meningovascular syphilis, or neurosyphilis presenting with cerebrovascular phenomena, has been described in studies primarily from the pre-antibiotic era as occurring several years after primary infection, although contemporary reports indicate it is often seen now as an early complication of infection.[8,13] Strokes are thought to occur as a result of an inflammatory vasculopathy in the setting of subacute to chronic meningeal inflammation and can affect both large and small vessels. The true prevalence of meningovascular syphilis in patients experiencing strokes is unclear, as studies reporting serologic evidence of syphilis in those admitted for strokes can be difficult to interpret, especially in high incidence settings. For example, a study of patients presenting with ischemic stroke in Thailand found that 8.4% had positive serum serologic testing and 2.5% met their definition of symptomatic neurosyphilis, although 71% had documented atherosclerotic risk factors, raising the possibility that the positive serologies were incidental and unrelated to the underlying mechanism of strokes.[14]

Late stages of neurosyphilis classically appear years to decades after primary infection and involve lesions of the cerebral parenchyma or spinal cord. Although they still occur, they are less commonly encountered in modern practice. General paresis is a progressive form of syphilitic encephalitis and presents with neuropsychiatric manifestations and cognitive decline.[9] Tabes dorsalis refers to the demyelinating posterior column myelopathy that occurs with late stage neurosyphilis. Symptoms include ataxic gait, loss of proprioception with impaired sensation, lancinating pains, bowel/bladder dysfunction, and paraparesis with abnormal reflexes.[9] Argyll Robertson pupils, defined as pupils that constrict when focusing on a near object but not in response to light, can be seen with any form of late neurosyphilis and are a frequent finding in patients with tabes dorsalis.[10] Gummas are mass-lesions composed of an inflammatory infiltrate and can be initially misdiagnosed as neoplasms on imaging.[15]

Diagnosis

The diagnosis of syphilis relies primarily on interpretation of different combinations of treponemal (eg, treponema pallidum particle agglutination [TPPA], chemiluminescent immunoassay [CIA], or enzyme immunoassay [EIA]) and non-treponemal (eg, rapid plasma reagin [RPR] and venereal disease research laboratory [VDRL]) tests.[16] Treponemal tests are specific to *T. pallidum* antigens and generally remain positive for life after infection, whereas non-treponemal tests develop in response to nonspecific lipoidal antigens and rise and fall in response to *T. pallidum* disease activity. The primary limitation of nontreponemal tests is the relatively common occurrence of biologic false-positive results in the absence of *T. pallidum* infection, although these tend to be of relatively low titer.[17] In patients with evidence of prior syphilis infection, a 4-fold increase in nontreponemal titers is a significant change that suggests a new infection.[16] Different testing strategies can be used to establish a diagnosis of syphilis, beginning either with the non-treponemal serology followed by confirmation with treponemal testing ("traditional algorithm") or starting with a high throughput treponemal assay (CIA/EIA) followed by a quantitative nontreponemal serology ("reverse algorithm"). Figure B outlines different permutations of these testing strategies.

Diagnosing neurosyphilis in a patient with serum evidence of active syphilis can be challenging and involves careful interpretation of CSF studies (Fig C). Most cases of neurosyphilis are associated with a lymphocytic pleocytosis as well as elevations in CSF protein. The degree of pleocytosis varies, with a cutoff of > 5 white blood cells (WBCs) per microliter suggested to be sensitive for the diagnosis of neurosyphilis.[9] In persons living with HIV (PLWH), a higher cutoff of > 20 WBCs per microliter is utilized, as untreated HIV itself can lead to a modest pleocytosis in the absence of neurosyphilis.[18] The incidence of CSF abnormalities in PLWH may be higher in patients with elevated nontreponemal tests (eg, ≥ 1:32) and those with CD4 counts ≤ 350 cells/μL.[17]

In addition to the careful interpretation of CSF parameters, diagnosing neurosyphilis involves application of different serologic tests to the CSF. The CSF VDRL, a nontreponemal test, is the gold-standard test for diagnosing neurosyphilis and is the only US Food and Drug Administration (FDA) cleared test for that indication. The CSF VDRL is relatively specific, but sensitivity is imperfect and has been suggested to range from 49% to 88% across various studies.[9] Alternative nontreponemal tests have been evaluated, specifically the CSF RPR, which was not found to have any improvement in sensitivity when compared to the CSF VDRL.[19] CSF treponemal tests (most commonly the CSF fluorescent treponemal antibody absorption [FTA-ABS]) have been suggested to be more sensitive but less specific than the CSF VDRL, and CDC guidelines recommend using them to exclude a diagnosis of neurosyphilis in complex cases where the likely cause is something other than neurosyphilis.[16]

More recently, studies have explored the role of molecular testing for the diagnosis of neurosyphilis. Sensitivities of different polymerase chain reaction (PCR) assays have been reported to range from 40% to 70%, depending on the specific assays and reference standards utilized in the studies[20]; consequently, PCR assays are not widely used for the diagnosis of neurosyphilis. Although there have similarly been reports of metagenomic next generation sequencing being used to diagnose

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neurosyphilis, the role of this technique in diagnosing low abundance pathogens like *T. pallidum* is unclear and likely relatively limited.[21]

CSF testing plays a limited role in patients with suspected otic or ocular syphilis and is not recommended in the 2021 CDC guidelines. The rationale for this recommendation is primarily based on studies which show relatively high rates of normal CSF parameters in both otic and ocular syphilis, such that a normal CSF examination would be insufficient to exclude their diagnosis in a patient with compatible signs/symptoms and positive serum testing.[16] Some experts still suggest CSF examination in certain patients with otic or ocular syphilis, however, the presence or absence of CSF abnormalities may provide prognostic information about vision/hearing recovery.[22,23]

Treatment

In contrast to many other bacterial infections, *T. pallidum* retains susceptibility to penicillin despite decades of use. The first-line treatment for neurosyphilis continues to be high-dose (18–24 million units per day) intravenous (IV) penicillin, for a duration of 10 to 14 days.[24–26] While never studied in rigorous comparative trials, the primacy of this regimen is supported by decades of clinical experience and the theoretical benefit of achieving higher CSF drug levels than with standard intramuscular (IM) preparations of penicillin. The primary alternative option historically has been procaine penicillin G (2.4 million units IM once daily) plus probenecid (500 mg orally 4 times per day) for 10 to 14 days, which has been shown to achieve higher CSF levels than single drug IM therapy alone; this regimen performed similarly to IV penicillin in a 2020 retrospective study of patients with neurosyphilis from Washington State, although it is not currently available in the United States at the time of this article's writing.[27]

The penicillin-based regimens of 10 to 14 days for neurosyphilis lead to shorter durations of drug exposure than regimens for late-latent syphilis, for which 3 weekly doses of IM benzathine penicillin G (BPG) are administered. Some experts recommend adding additional doses of IM BPG after a standard neurosyphilis course.[24] Clinical data to support this practice is lacking, however. Especially in the context of recent penicillin shortages, we would recommend against routine use of additional doses of IM BPG following a standard course of IV penicillin for the treatment of neurosyphilis.

Ceftriaxone is a third-generation cephalosporin commonly used for other CNS infections and has activity against *T. pallidum*. It is included as a primary alternative regimen (at a dose of 1–2 g IV daily for 10–14 days) by guidelines from the European Union and United Kingdom, whereas it is included as a consideration in the United States CDC guidelines for patients with penicillin allergy.[24–26] A 2021 retrospective study from France evaluated outcomes of patients with early neurosyphilis at 8 centers from 1997 to 2017 who were treated with ceftriaxone (42 patients) or IV penicillin (166 patients). Overall clinical response (ie, patients with complete or partial response) occurred significantly more commonly in the ceftriaxone group (98% vs 76%), a difference that was maintained after propensity score weighting. Complete and serologic responses, however, were similar between groups. Although not a prospective clinical trial, this observational study suggests that ceftriaxone is similarly effective to IV penicillin for the treatment of neurosyphilis.[28]

Some have suggested the use of high dose doxycycline (200 mg twice daily for 28 days) for the treatment of neurosyphilis given its oral formulation, activity against *T. pallidum*, and CSF penetration; it is included as an alternative treatment regimen for neurosyphilis by the UK guidelines but not the US or European guidelines.[25] Data for this approach are quite limited and rely primarily on small retrospective series in patients with neurosyphilis and ocular syphilis.[29,30]

For patients with penicillin allergy, guidelines recommend either ceftriaxone or penicillin desensitization.[24–26]

Monitoring and Follow-up

Patients being treated for neurosyphilis should have a nontreponemal test drawn in close temporal proximity to initiation of treatment, with subsequent clinical and serologic evaluation performed at 6, 12, and, if late disease, 24 months thereafter; more frequent monitoring may be considered in individuals at higher risk for reinfection or difficult follow-up.[24] A successful serologic response to treatment is suggested by a 4-fold decline in titer by 12 months for early syphilis and 24 months for late syphilis or syphilis of unknown duration.[24] Although some patients may fully serorevert (ie, the nontreponemal titers turn negative), many will continue to have low-positive nontreponemal titers following treatment, referred to as a "serofast" state.

The question of whether to repeat a CSF examination for patients following treatment for neurosyphilis has evolved in recent years. Prior guidelines recommended repeat LP every 6 months following treatment to document resolution of the pleocytosis. This dogma has been challenged by more recent studies in immunocompetent patients and PLWH on antiretroviral therapy suggesting that normalization of the RPR predicts a favorable response of CSF abnormalities; consequently, the 2021 CDC guidelines no longer recommend routine CSF

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examination following treatment of neurosyphilis for all patients.[24,31]

Conclusions

Recent years have seen dramatic increases in rates of infection with *T. pallidum*, currently at levels not seen since the 1950s. In the context of this epidemic of syphilis, clinicians need to remain vigilant for the dreaded complications of this disease, including its myriad neurologic manifestations. Neurosyphilis can occur at any stage of infection with *T. pallidum*, and the spectrum of clinical manifestations ranges from asymptomatic neuroinvasion to devastating syndromes of progressive parenchymal destruction. Diagnosis relies on interpretation of serum and CSF serologic studies in the appropriate clinical context, and treatment regimens have changed little in the past several decades. Far from a disease of the past, neurosyphilis continues to be an important contemporary CNS infection, and neurologists should maintain a high index of suspicion and be aware of when to consider this on their differential diagnosis and how to interpret serologic testing to make the diagnosis.

Acknowledgments

None.

Author Contributions

Daniel J. Minter: Conceptualization; writing – original draft; writing – review and editing. **Felicia C. Chow:** Conceptualization; writing – original draft; writing – review and editing; supervision.

Potential Conflicts of Interest

Neither D.J.M. nor F.C.C. have any conflicts of interest to disclose.

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