Management: Definition of Drug Resistant or Pharmacoresistant

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I. Drug Resistant Epilepsy – A concept with multiple names
   a. Pharmacoresistant epilepsy
   b. Drug resistant epilepsy
   c. Treatment resistant epilepsy
   d. Medically refractory epilepsy
   e. Medically intractable epilepsy

II. Drug Resistant Epilepsy – A concept with multiple definitions(1)
   a. Applying definitions utilized in several different studies in a cohort of 13 children identified rates of drug resistance (intractability as termed in the study) between 9%-24%
   b. Agreement between these studies was variable
      i. An overall absolute agreement between any two methods was >80%
      ii. Kappa statistics had a much higher variability ranging from as high as 0.79 (excellent agreement) to as low as 0.39 (poor agreement)

III. Why is a formal definition even required?
   a. Variability potentially limits comparisons between centers and studies
      i. The study above illustrates the differences in identification and thus the challenges in comparisons across methodologies(1)
   b. Provides a framework for future research on the phenomenon of drug resistance
      i. Future research may allow for other methods of identifying drug resistance
      ii. Like other classification systems, this definition will likely need to be modified over time

c. Clear diagnostic criteria can aid in establishing evidence-based guidelines in the future to facilitate treatment

IV. "Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."(2)

a. The concept of an adequate (or informative) trial of an anti-epileptic drug
    i. Appropriately chosen anti-epileptic drug(2)
        1. Not all anti-epileptic drugs are appropriate for all epilepsy syndromes
        2. Utilizing anti-epileptic drugs for which data do not exist to support their efficacy for a given syndrome/seizure type would likely not be considered an appropriate anti-epileptic drug choice.
    ii. Adequate utilization of the anti-epileptic drug(2)
        1. An anti-epileptic drug should be utilized for a long enough time period to assess efficacy
        2. An anti-epileptic drug should be utilized at a reasonable dose during the trial
            a. Titration rate and final dose are both important considerations
            b. Serum levels can clarify whether an adequate dose to potentially achieve a therapeutic was being utilized
        3. Patient compliance with the regimen is also an important factor
            a. Blood levels along with patient reporting can help to assess compliance
    iii. What was the response to the anti-epileptic drug trial (i.e. why was the drug stopped)(2)
        1. Continued seizures
        2. Adverse effects
        3. Patient preferences
            a. Financial
            b. Family planning
        4. Unknown

b. If an anti-epileptic drug was appropriate for the epilepsy syndrome/seizure type(s) and was tried at a sufficient dose with documented therapeutic levels but was discontinued because of continued seizures, this would be an informative (or adequate) trial and failure of this medication would be counted toward failure of two anti-epileptic drugs(2)
c. If an anti-epileptic drug was stopped two weeks into a titration due to intolerable adverse effects, this medication would not typically be counted as a failure of anti-epileptic drug(2)
    i. The drug failed from a tolerability standpoint
    ii. The drug did not clearly fail from an efficacy standpoint (i.e. seizure control) as it was not at a dose where effectiveness could clearly be assessed
    iii. This definition of failure lends itself to a patient potentially failing many anti-epileptic drugs but only a much smaller subset may meet the criteria for an informative or adequate trial

V. The concept of seizure freedom
    a. In assessing seizure freedom, often certain types of “non-disabling” seizures are allowed while still categorizing a patient as seizure free
    b. For this definition, they propose a definition of seizure freedom that is freedom from all seizures including auras
    c. To be considered seizure free, there should be no seizures for 12 months or three times the longest pre-treatment inter-seizure interval (whichever is longer)(2)
        i. The duration of three times the longest inter-seizure interval is based upon the “rule of three”
        ii. For patients with very infrequent seizures, this can lead to a long interval before a statement about response to a treatment can truly be made
        iii. If a patient has been seizure free for longer than three times the longest inter-seizure interval but less than 12 months, they should be considered “undetermined” as to the response to treatment

VI. The evidence for failure of two anti-epileptic drugs as the cutoff for drug resistance
    a. Children
        i. 466 children between 1 month and 15 years of age with new onset epilepsy recruited from four Dutch hospitals(3)

1. Overall outcomes at 5 years
    a. 55% were seizure free for the previous 3 years
    b. 64% were seizure free for at least 2 years
    c. 76% were seizure free for at least 1 year
2. 86% (388) children were treated with one or more anti-epileptic drugs
    a. 53% had one anti-epileptic drug
    b. 47% had two or more anti-epileptic drugs
    c. Children achieving at least one year of seizure freedom at five years out
        i. 46% of children on one anti-epileptic drug
        ii. 19% of children on two anti-epileptic drugs
        iii. 9% of children on three or more anti-epileptic drugs

ii. 613 children between 1 month and 16 years of age with new onset epilepsy recruited from pediatric neurologist offices in Connecticut(4)
1. 21% (128 children) did not have a remission of >1 year on 2 anti-epileptic drugs
    a. 57% of these children experienced a remission of at least one year following failure of the second anti-epileptic drug
    b. 38% of these children were in remission at the time of last contact for one year
    c. 22% of these children were in remission at the time of last contact for at least three years

iii. 120 children between 1 and 18 years of age seen in the outpatient clinics at Children's Hospital of Philadelphia for temporal lobe epilepsy(5)
1. 61.6% of children were seizure free following the first anti-epileptic drug trial
2. 10.8% of the children that continued to have seizures after the first anti-epileptic drug became seizure free with trials of additional anti-epileptic drugs

b. Adults and Children
i. 525 patients between 9 and 93 years of age with new onset epilepsy recruited from the Epilepsy Unit in Glasgow, Scotland(6)

1. 470 were never treated with an anti-epileptic drug previously
    a. 47% were controlled with the first anti-epileptic drug
    b. 13% were controlled with the second anti-epileptic drug
    c. 4% were controlled following the third anti-epileptic drug or multiple anti-epileptic drugs
2. The overall rate of remission (at least one year) was 63%

ii. 780 patients between 9 and 93 years of age with new onset epilepsy recruited in Glasgow, Scotland(7)
1. 64.6% (504 patients) became seizure free for at least 12 months
    a. 79% remained in remission until the end of follow-up
2. Of the 504 patients responding to anti-epileptic drugs
    a. 78% responded to the first anti-epileptic drug
    b. 11% responded to the second anti-epileptic drug
    c. 2.3% responded to subsequent trials of monotherapy
    d. 7.9% responded to duotherapy regimens
    e. 1 patient responded to a three drug regimen
    f. 1 patient responded to a four drug regimen

iii. 246 patients between 12 and 83 years of age identified from the University of Pennsylvania Epilepsy Center(8)
1. Patients had to have failed two or more anti-epileptic drugs
2. Patients had to have at least one seizure per month over the three months prior to the study index date
3. 15% attained a six month seizure remission and were seizure free by the end of the period of observation
4. 11% (26 patients) became seizure free associated with a change in anti-epileptic drug treatment
    a. 18 with the addition of an anti-epileptic drug
    b. 7 with a dose change in an anti-epileptic drug
    c. 1 with both the addition of and a dose change in an anti-epileptic drug

iv. 478 patients 12 years of age or older were identified from the Rambam Medical Center(9)

1. 61.8% of 110 patients never previously treated with an anti-epileptic drug became seizure free during the follow-up period
2. 41.7% of 127 patients treated with a single previous anti-epileptic drug became seizure free during the follow-up period
3. 16.6% of 253 patients treated previously with 2-5 anti-epileptic drugs became seizure free during the follow-up period
4. 0% of 29 patients previously treated with 6-7 anti-epileptic drugs became seizure free during the follow-up period

c. Adults
    i. 155 patients between 19 and 80 years of age recruited from a single outpatient clinic in London(10)
        1. Patients had active epilepsy (one or more seizures per month) with a history of epilepsy for at least five years
        2. 17% were seizure free following the addition of one previous untried anti-epileptic drug
        3. 70 patients that did not respond to the addition of one anti-epileptic drug underwent a subsequent anti-epileptic drug trial
            a. 14% were seizure free after the second new anti-epileptic drug was added
        4. 27 patients that did not respond to the addition of a second anti-epileptic drug underwent a subsequent anti-epileptic drug trial
            a. 15% were seizure free after the third new anti-epileptic drug was added

VII. Where does this definition leave the epilepsy community? Limitations and future directions
    a. The authors proposed this as a working definition with the hope and expectation that further refinements would occur over time
        i. The dynamic course of anti-epileptic drug response was identified as an area of limited knowledge(2)
            1. Further advances in our understanding of these dynamics may allow for more nuanced definitions in the future

ii. The contributing factors for developing drug resistance (or for drug responsiveness) are not addressed in this definition (2)
    1. The authors suggest that a common definition of drug resistance may facilitate identification of these factors

b. Practical challenges
    i. Determining the adequacy of a previous anti-epileptic drug trial can be difficult
        1. Adequate documentation and adequate recollection may not be possible
        2. Understanding the impact of adverse events on the decision to change anti-epileptic drugs may be very challenging
    ii. This definition of drug resistance is focused solely on seizure freedom
        1. Other outcome assessment measures are not considered in this definition but still require careful consideration
        2. Patient-centered care efforts, particularly in the United States, focus increasingly on the patient/family perceptions of care and overall satisfaction which is rarely limited to a single domain (i.e. not considering just whether seizure free or not)
            a. Patient/family preferences due to any number of factors may lead to a desire to conceptualize care goals around other factors making application of this definition more challenging

c. Pragmatism
    i. Definitions, like all aspects of medical literature, need to be considered in the context of an individual patient
    ii. Educating patients and family members on how one arrives at a diagnosis of drug resistant epilepsy is a critical part of care
    iii. Improved understanding will often translate to improved compliance

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